RANDOMIZED CONTROLLED TRIAL OF THE STOOL DNA TEST TO IMPROVE COLORECTAL CANCER SCREENING AMONG ALASKA NATIVE PEOPLE (NCT04336397)

Principal Investigator: Diana Redwood, PhD MPH.[1]

Consultants: Mark Thorndike, MD;[2] James Tiesinga, MD; [2] John Kisiel, MD; [3] Lila Rutten, PhD; [3] Judith Kaur, MD; [3] Peter Holck, PhD.[4]

[1]Alaska Native Tribal Health Consortium, Anchorage AK.

[2]Alaska Native Medical Center, Anchorage AK.

[3]Mayo Clinic, Rochester MN and Jacksonville FL.

[4]Holck Consulting, Anchorage AK

TABLE OF CONTENTS

ABSTRACT

Background: Only 59% of Alaska Native (AN) people have been adequately screened for colorectal cancer (CRC), despite having the highest reported burden of CRC in the world. A new take-home noninvasive screening method is now available, the multi-target stool DNA test (MT-sDNA; Cologuard) which includes a novel patient navigation system. However, MT-sDNA has not been tested for feasibility and acceptability within the Alaska tribal health care delivery system, and it is unknown whether use of this new test will increase AN screening rates. Addressing this unmet need will help us better understand what CRC screening methods work best in rural/remote tribal and underserved communities.

Objective: This research study will pursue two specific aims: (1) identify patient-, provider-, and system-level factors associated with CRC screening preferences, uptake, and follow-up; and 2) test the hypothesis that multi-level high and medium intensity MT-sDNA community-based interventions, as compared with usual care, will increase CRC screening rates among AN people in rural/remote communities.

Methods: For the first aim, focus groups and interviews of AN people who are non- or inadequately adherent to CRC screening guidelines and their healthcare providers will be used to identify individual, interpersonal (provider), and health system factors for future intervention. For the second aim, a three-arm cluster randomized controlled trial (high intensity with patient navigation, medium intensity with mailed reminders, usual care) will provide evidence on the usefulness of MT-sDNA in remote AN communities as well as the first data on MT-sDNA adherence rates in the AN population.

Conclusion: The results of this study will help inform clinical practice and policy throughout the ATHS. We will gather evidence to support best practices for CRC screening implementation among AN people and create a baseline for future research to increase CRC screening utilization and access among AN people.

1. INTRODUCTION

Alaska Native (AN) people have among the highest rates of colorectal cancer (CRC) in the world. Both incidence of and mortality from CRC is **twofold higher among AN people** than US whites; this disparity has persisted for over 40 years.[1] CRC is the second most frequently diagnosed cancer and the second leading cause of cancer-related death for ANs.[2]

Preventing CRC is an important health priority of AN tribal health leaders and communities. Screening can prevent CRC through the identification and removal of colorectal polyps before they develop into cancer. Screening also allows for the detection and diagnosis of CRC at earlier stages, when treatment has greater likelihood of success with lower impact on quality of life.[3-5]

In Alaska, CRC screening, including colonoscopy, is a covered service for AIAN beneficiaries, although screening-related travel is not always covered. Due to the geographic and health care delivery challenges of CRC screening in Alaska, only 59% of AN people have been adequately screened for CRC; and AN screening rates remain persistently lower than national rates.[6] Efforts to increase CRC screening among AN people have led to some successes, but screening rates still vary substantially by Alaska Tribal health regions, ranging from less than 30% to 73%.[7]

Complicating the ability to increase screening is that AN people have a high prevalence of *Helicobacter pylori* infection-related gastrointestinal bleeding[8,9] which is associated with higher false positive rates for guaiac-based fecal occult blood testing (gFOBT).[10] Consequently, gFOBT is not recommended for CRC screening in the AN population.[11] The fecal immunochemical test (FIT), another take home stool test, is available in some regions of Alaska, but because of the high rates of precancerous polyps and CRC, colonoscopy has been the preferred method for CRC screening in the ATHS.[11] However, colonoscopy presents logistic and access challenges. Substantial resources, including time; travel expenses for the patient and a medical escort to a regional hospital or to Anchorage, usually by small aircraft; and specially trained personnel and facilities are required for colonoscopy within the ATHS.[12,13] Only half of the regional Tribal hospitals offer colonoscopy year-round; the others hold several weeklong screening clinics per year. Furthermore, colonoscopy is biased toward detection of distal disease,[14-20] with limited or minimal effect on incidence or mortality of proximal CRC.[17,22,21] This is of concern as over 41% of CRCs in AN people occur in the proximal colon.[2] Therefore, logistical barriers, endemic occult GI bleeding, and suboptimal test performance limit the value and practicality of current CRC screening approaches in the AN population.

New screening methods are urgently needed to improve screening in this population. Recently, the take-home multi-target stool DNA test (MT-sDNA; Cologuard®, Exact Sciences, Madison, WI) has emerged as a viable alternative to other screening tests.[22,23] Approved by the FDA and CMS for commercial use in 2014, the MT-sDNA test detects 11 colorectal neoplasia-associated DNA biomarkers, including two DNA methylation markers [*NDRG4*, *BMP3*], seven point mutations on K-*ras*, quantitative DNA using *ACTB* [β-actin], continuously shed in human feces or stool as well as the presence of fecal hemoglobin.[24] MT-sDNA sensitivity for CRC is higher than other take home tests, is similar to that reported by colonoscopy, provides consistent detection of both left- and right-side colon cancers, and has the benefit of an embedded patient navigation system to help address patient and health system barriers.[25-27,32] As with other noninvasive fecal CRC screening tests (gFOBT, FIT), a positive result may indicate the presence of CRC and requires follow up with a diagnostic colonoscopy. Initial MT-sDNA studies have shown its use increases screening adherence, including among never-screened patients, and may actually increase the yield and quality of follow-up colonoscopies.[25-27] However, it is unknown whether the use of MT-sDNA would increase adherence to CRC screening among AN people and what its acceptability is compared to other available screening tests.

This study will address this gap by providing a multi-level, quantitative intervention exploring use of the MT-sDNA test for CRC screening among AN people, complemented by qualitative evaluation of individual and health system CRC screening barriers reported by “never screened” and “non-adherent to guidelines” AN patients and their healthcare providers.

1.1. SPECIFIC AIMS

Aim 1. Identify patient-, provider-, and system-level factors associated with CRC screening preferences, uptake, and follow-up, using a theory-based, mixed methods multi-stakeholder formative and process evaluation. While our prior work shows that an intervention to improve screening is likely to be broadly feasible and accepted, we anticipate variation in adherence between communities. To identify reasons for that variation we propose to:

Sub-aim 1.a. Conduct a formative evaluation to assess community context and engage stakeholders in MT-sDNA intervention development including study design, protocol development, and implementation.

Sub-aim 1.b. Use the Health Belief Model[28,29] to evaluate patient-level factors associated with test preference, screening adherence, and diagnostic follow-up.

Sub-aim 1.c. Conduct patient key informant and focus group interviews to identify factors that facilitate and impede screening uptake and effects among subgroups (sex, age, degree of rurality).

Sub-aim 1.d. Conduct a brief survey and key informant interviews among community health aides, providers, and tribal health system administrators using validated measures of intervention feasibility, acceptability, and appropriateness[30] to characterize provider- and system-level barriers and promotors to MT-sDNA implementation.

Aim 2. Test the hypothesis that multi-level high and medium intensity MT-sDNA community-based interventions, as compared with usual care, will increase CRC screening rates among AN people in rural/remote communities.

Sub-aim 2.a. Participants receiving high intensity intervention (navigated tribal health worker outreach, a mailed MT-sDNA kit, culturally appropriate educational material, and follow-up reminders) are expected to have a 20% increase in screening uptake while those receiving medium intensity intervention (mailed culturally appropriate educational material describing CRC screening options available, including MT-sDNA, and navigated follow-up outreach reminders) will have a 10% increase in screening uptake over those receiving usual care (screening recommendation at a clinic visit). A sample of 770 participants in at least six communities per study arm will be recruited.

Sub-aim 2.b. Measure the impact of sex, age, and rurality on the effect size of the intervention, MT-sDNA uptake compared to colonoscopy, and MT-sDNA follow up to diagnostic colonoscopy.

Sub-aim 2.c. Measure MT-sDNA sample quality and neoplastic yield in remote AN communities. We anticipate that the proportion of MT-sDNA tests meeting quality control standards will be the same as in the general US population (96%) and that pre-cancerous polyp detection rates at diagnostic post-MT-sDNA colonoscopy will exceed routine clinical practice rates in the general US population (52%-67%).

1.2 RATIONALE AND SUPPORTING DATA

MT-sDNA represents a potential addition to CRC screening among AN people; it is accurate, easy to use, unencumbered by diet/medication restrictions, and may be accessible from low resource, underserved sites. However, MT-sDNA has not been tested in the ATHS practice setting. In addition, our study design will allow us to separate the effects of different technology: mailed reminders with small media health communication vs. telephone outreach by a patient navigator. We will also gain important new insight and qualitative data on the "never" and "rarely screened" population to identify strategies to improve screening in these vulnerable groups, as recommended in the 2017 American Indian and Alaska Native Collaborative CRC Screening Strategic Framework.[31]

In **Specific Aim 2**, we will evaluate (using a three-arm randomized controlled trial (RCT) design) the efficacy of graded intensity interventions for increasing CRC screening uptake as well as determine the MT-sDNA repeat adherence rate among AN people. Because the MT-sDNA test has only been available commercially since 2014, there are no published data available on repeat adherence to screening using

MT-sDNA. Adherence to guidelines is a critical component of the success of screening programs: failure to screen at appropriate intervals or follow up on abnormal results within a timely manner have been associated with substantially increased odds of CRC mortality.[32] By determining MT-sDNA adherence to screening, this study will contribute to the evidence base for this new screening test, which has implications for system workloads and patient outcomes. The design of the intervention arms: high intensity patient navigation and medium intensity AN-specific health education materials, compared with usual clinical practice, was chosen based on our previous work[13,33] and that of others[34-38] demonstrating the benefit of these methods in increasing screening adherence.

The qualitative data collected in **Specific Aim 1** will complement the RCT intervention by determining promoters and barriers to CRC screening practices among screening non-adherent AN patients and their healthcare providers in the ATHS. This will provide a patient- and provider-centered viewpoint on reasons for non-adherence to CRC screening that will lead to new areas for screening promotion. Screening test acceptability is an important factor for increasing CRC screening rates.[39]

Patient willingness and ability to complete tests at home as well as provider recommendation are major factors in the effectiveness of a stool test-based CRC screening program.[40-44] Many barriers and facilitators are screening test-specific such as fear of pain associated with colonoscopy, or discomfort with collecting stool samples.[45] Even when cost is removed as a barrier, there are still issues for patients that remain.[46] There may also be specific Tribal and cultural barriers to CRC screening, including lack of AIAN healthcare providers or patient navigators, health education materials that are not culturally relevant, or health literacy issues and English as a second language among AIAN elders.[47,48] To begin to understand these barriers from the AN perspective, we will conduct a series of focus groups and key informant interviews with screening non-adherent and inadequately adherent AN patients from Anchorage and rural areas. These will be supplemented by a series of key informant interviews with healthcare providers from across the ATHS that are involved in the promotion and delivery of CRC screening. Interviewees may range from Community Health Aides/Practitioners that provide primary healthcare in rural villages, to surgical staff at ANMC. Ultimately, identifying areas for system improvement through our quantitative analysis will have little impact if proposed solutions are infeasible or unacceptable to the population served. Thus, the goal of this Specific Aim is to identify culturally appropriate, AN-identified opportunities for screening promotion that enhance the chances of successful implementation and CRC screening uptake.

The field of behavioral economics shows us that there is sometimes a considerable gap between what people say they will do versus what they actually do.[49,50] This intervention will demonstrate which outreach practices actually lead to increased screening, and whether the addition of MT-sDNA substantially increases screening rates in the AN population. This intervention trial is specifically designed to address CRC screening barriers identified through our previous work, while also laying the foundation for interventions in the future. In summary, this research will address a health disparity of established community concern, and generate data that will have broad-reaching clinical and policy outcomes for the ATHS. This study will advance scientific knowledge and clinical practice by revealing strategies that work to increase screening among the AN population and help curb the extreme, disparate morbidity and mortality due to CRC in this population.

2. STUDY DESIGN AND APPROACH

2.1 STUDY TEAM

Key Personnel:

Study PI: Diana Redwood, PhD	Senior Epidemiologist, ANTHC

Consultants:

Clinical Consultant: Mark Thorndike, MD	Chief of Surgery, ANMC

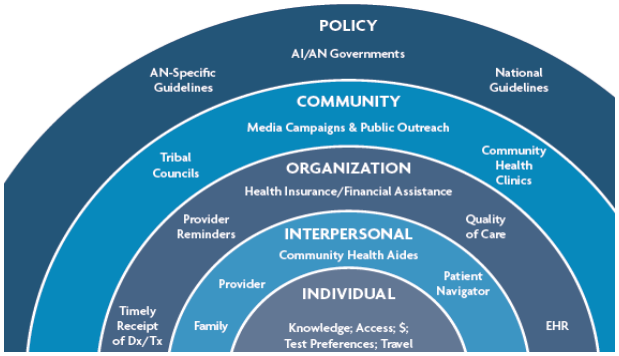
Clinical Consultant: James Tiesinga, MD	Pathology Lab Director, ANMC
Consultant: Lila Rutten, PhD	Professor, Mayo Clinic
Consultant: John Kisiel, MD	Gastroenterologist, Mayo Clinic
Consultant: David Ahlquist, MD	Gastroenterologist, Mayo Clinic
Consultant: Judith Kaur, MD	Professor, Mayo Clinic
Biostatistician: Peter Holck, PhD	Consultant, Holck Consulting

Other Personnel:

Qualitative Data Expert	ANTHC EpiCenter Staff
Statistician/Data Manager	ANTHC EpiCenter Staff
Study Coordinator	ANTHC EpiCenter Staff
Research Assistant	ANTHC EpiCenter Staff
Media Specialist	ANTHC EpiCenter Staff

2.2 THEORETICAL FRAMEWORK.

Figure 1. Study Social Ecological Model.



The theoretical basis for our intervention is the CDC's CRC Control Program Social Ecological Model (SEM, Figure 4),[51,52] supplemented by the Health Belief Model.[28,29] We have successfully applied these in our previous work.[34,53] Health behavior constructs include perceived severity, perceived susceptibility, perceived benefits, perceived barriers, and self-efficacy. These beliefs may interact with system-level factors, including the healthcare delivery system's approach to CRC screening.[54,55] Our study is designed to examine individual, interpersonal, and organizational level predictors associated with CRC screening. Our study will have a sequential explanatory mixed methods design.[56,57] This will include a randomized controlled trial complemented by qualitative focus groups and key informant interviews. The qualitative findings will be used to help explain and triangulate the quantitative results; however, the quantitative and qualitative data will be kept analytically distinct. Statistical techniques will be used to analyze screening adherence data while thematic analysis will be used to analyze interview data. In this way, the integrity of each method will be preserved while capitalizing on the potential for enhanced understanding from combining the two sets of findings.[56]

This study will also use the Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) Framework[58] to inform the study design and implementation activities (see Figure 2).

Figure 2. Reach, Effectiveness, Adoption, Implementation, Maintenance Framework outcomes and assessment approaches used in the study design.

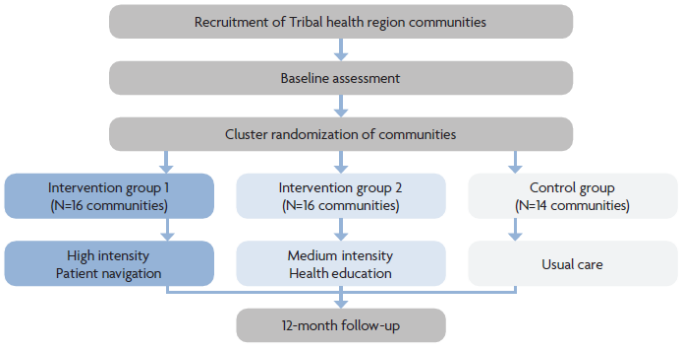
RE-AIM Construct	Definition	Relevant Outcomes	Assessment Approach and Timeline
Reach	Number, proportion, and representativeness of individuals who participate in the intervention.	Proportion of eligible patients who return MT-sDNA kit	Total number of patients who were sent and returned MT-sDNA kits.
Effectiveness	Intervention effect on targeted outcomes.	Proportion of abnormal MT-sDNA screens who follow up with diagnostic colonoscopy	Impact of intervention on overall CRC screening rates; Rates of follow-up diagnostic colonoscopy among persons receiving abnormal screen.
Adoption	Number, proportion, and representativeness of participating settings and providers.	Proportion of invited clinics who agree to participate	Proportion of clinics agreeing to participate initially and track attrition (if any).
Implementation	Extent to which the intervention is consistently implemented by staff members including feasibility, acceptability, and appropriateness.	Evaluate provider- and system-level barriers and promotors to MT-sDNA implementation.	Survey and key informant interviews among providers and administrators.*
	At the individual level, implementation refers to clients' use of the intervention strategies.	Evaluate factors that facilitate and impede screening uptake and effects among subgroups and examine differences by sex, age, degree of rurality.	Survey of non-adherent patients (Health Belief Model); Patient key informant and focus group interviews.
Maintenance	The extent to which a program or policy becomes institutionalized or part of the routine organizational practices and policies.	Proportion of practices who adopt MT-sDNA screening strategies after study period	Calculate proportion of participating practices that opt to adopt clinical practice change informed by study results.

Adapted from Glasgow RE, McKay HG, Piette JD, Reynolds KD. The RE-AIM framework for evaluating interventions: What can it tell us about approaches to chronic illness management? *Patient education and counseling* 2001;44(2):119-127.*12-item Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) to assess system-level context prior to implementation (Weiner et al. 2017).

2.3 Study Site, Data Sources and Study Population

Study design: Under Aim 1, the study will employ focus groups and key informant interviews to learn about factors associated with screening response. Under Aim 2, the study will employ a cluster-randomized design, in which twelve communities within 1-2 Tribal health regions will be randomized to one of the two study intervention conditions (16 communities per intervention), matched by community size (Figure 3). Clinic staff (front desk, Community Health Aides, midlevel providers) in intervention communities will be informed that a CRC outreach project is occurring in case they are contacted by community members but not which arm their community is in. All AN adults aged 45-75 within each community will be offered the same intervention. This design will reduce the likelihood of study contamination from having individuals in a small community be offered different screening options, as well as be more culturally acceptable to AN people.[59] The high intensity intervention will include navigated outreach, a mailed MT-sDNA kit, mailed culturally appropriate educational material describing CRC screening options available and follow-up reminders (Study Group 1). The medium intensity intervention will include mailed culturally appropriate educational material describing CRC screening options available, including MT- sDNA, and navigated follow-up outreach reminders (Study Group 2). All other communities in the participating Tribal health region will serve as the reference group (Study Group 3) receiving usual care (i.e., screening recommendation at a clinic visit).

Figure 3. Study cluster randomization design.



Study outcomes: The **primary outcome measure** as determined by electronic medical record review by a study team member blinded to randomization assignment will be completion of an incident CRC screening episode. This will be defined as having at least one of the following within 1 year of follow-up after randomization and intervention: colonoscopy; MT-sDNA with a negative result; or MT-sDNA with

a positive result followed by a colonoscopy within 90 days. Due to the COVID-19 pandemic preventive screening was postponed for a time, which created a backlog of patients who need screening, including screening for CRC. To adjust for this delay, additional medical record review will be conducted to assess for any incident CRC screening episode within 18-months after randomization and intervention. A **secondary outcome measure** will include the rate of positive MT-sDNA test follow up to diagnostic colonoscopy. We anticipate that positive MT- sDNA tests will have higher follow-up rates to colonoscopy within 90 days than other studies have reported of positive FIT/gFOBT (55.6% followed up with colonoscopy)[54] due to the patient navigation system included in the MT-sDNA test model. We will also compare incident CRC and advanced adenoma [adenomatous polyp ≥1 cm or containing >25% villous component or high-grade dysplasia, or sessile serrated adenoma/polyp ≥1 cm] detection between the three arms. We will also incorporate into our secondary analyses measures from the process evaluation (e.g., patient satisfaction with MT-sDNA vs colonoscopy, provider attitudes and beliefs) as well as other moderating factors to determine their roles in explaining the magnitude and direction of the results we find.

Specific data elements collected on CRC screening clinical care will be pulled from tribal electronic medical records (EMR) and the ANMC CRC 1st Degree Relatives database, as well as data from the Alaska Native Tumor Registry (ANTR). Variables included in the EMR include: age, sex, race/ethnicity, history of CRC screening; personal or family history of CRC or polyps; test adherence; indication for test(s) (screening, surveillance, diagnostic); clinical diagnosis; biopsy/polypectomy performed; bowel preparation adequacy; cecum reached; recommended follow-up procedure(s); histology, size and number of polyp/lesions; follow-up surgery details; final diagnosis; recommended next screening/surveillance test and time interval; recurrent cancers; and status and date of cancer treatment. Variables collected will include those previously mentioned above, although there may be missing data for some of these variables in regional EMRs. Data included in the ANTR will only be used to fill in missing data to include cancer diagnosis and treatment dates, clinical information regarding the cancer (e.g., size, histology, morphology, laterality), and cancer treatment information (first course of treatment only). Data included in the CRC 1st Degree Relatives database will only be used to determine if a 1st degree relative with prior CRC was diagnosed at age 60 or younger if not available in the medical record.

2.4 Inclusion and Exclusion Criteria

Quantitative Study. **Inclusion Criteria:** The study will include AN adults ages 45-75 eligible to receive health care through the Alaska Tribal Health System that are active users (at least one Alaska Tribal Health System visit in the previous three years) and have contact information on file. **Exclusion criteria:** Participants will be ineligible if they have a history of familial adenomatous polyposis, hereditary non-polyposis CRC, previous colonoscopic evidence of inflammatory bowel disease, Crohn's disease, colorectal adenomas, CRC, presence of a 1st degree relative with prior CRC diagnosed at age 60 or younger, or positive fecal occult blood test in the last 6 months as these patients are not eligible for the MT-sDNA test. Patients adherent to screening (colonoscopy within 10 years, sigmoidoscopy within five years, or fecal occult blood testing within preceding 12 months) will also be excluded from the intervention trial.

Qualitative Study: We will recruit never or inadequately screened AN patients ages 45-75 and Alaska tribal health system providers to participate in either focus groups (patients only) or key informant interviews (patients and providers). We will recruit AN patients who have not been screened according to their tribal medical records at ANMC and at participating rural Tribal health organizations (THOs). Inadequately screened will be defined as patients who are not up-to-date with recommended screening. Clinical staff will be recruited based on their involvement in the provision of CRC screening at the participating organizations. During and following the graded intensity intervention, we will survey samples of patients to evaluate their awareness and response to the CRC intervention. The survey will be conducted by the Patient Navigator and/or the study Evaluation Consultant. They will need to know which screening test the patient had (colonoscopy or stool DNA test) so they can ask the survey

questions about how the patient felt about using that specific test, and why they chose that test over the other one. It is important they also know the test result so they can anticipate any questions the patient might have, especially if there was an abnormal finding. We will also conduct a semi-structured open-ended telephone survey with intervention participants who requested the MT-sDNA test for CRC screening, were sent a test kit but did not complete and return it to the laboratory for analysis within the 12-month post intervention period. The purpose of the survey is to learn about the underlying barriers and reasons patients did not complete this screening method. Similarly, we will survey patients who chose to complete screening with a colonoscopy, scheduled an appointment, but never completed a procedure to assess barriers to patients completing the procedure even after it was scheduled. A study staff member at ANTHC will contact patients and conduct the surveys. We will verify patients' address and phone number at the time of the surveys to assess whether we sent the kit to the correct address, which could relate to non-adherence of screening with the MT-sDNA test as well as update YKHC medical records with patients' current contact information. We will use IRB- and tribally-approved study flyers and information sheets located at the Alaska Native Medical Center in Anchorage, AK and participating rural THOs to further recruit participants per IRB and tribal review.

2.5 STATISTICAL ANALYSIS.

Although this study will use a cluster-randomized design with the community as the unit of analysis, our research experience in rural Alaska communities indicates minimal within community influence on an individual's personal health decisions. Because an intra-class correlation near zero approaches a simple random sample design, for clarity in our power calculations we have approximated our design as a simple random sample.[60] The sample size allocation for this study is based on a pre-specified ability to detect an expected difference of 10% or more in screening participation rates for usual care vs any intervention as well as a difference of 10% or more in screening for high intensity vs medium intensity outreach. Given these expected improvements in screening rates, and the expected non-intervention screen rate of 59% based on current rates among AN people, we anticipate more than 80% power to detect a statistically significant difference between screening rates in our medium and high interventions, at alpha of 0.05. To achieve this, we will recruit a sample of 775 or more persons per study arm. An intent-to-screen principle will be used to analyze all eligible patients for the primary outcome: screening participation. All eligible communities will be randomly assigned to an intervention arm at baseline. Group assignment will not be shared because all patients will be randomized at the same time point. Outreach patients will be blinded to the presence of alternate interventions; usual care patients will be blinded to the presence of group assignment altogether.

We will compare demographic characteristics (sex, age) between those screened using MT-sDNA and colonoscopy, as well as by intervention status (high intensity, medium intensity, usual care) in simple frequency tables. We will use multivariable models to assess the role of intervention status in determining screening rates, adjusting for potential confounders such as age, sex, and other demographic characteristics. Because our primary response is the proportion of persons screened (or the screening rate) we will utilize logistic and/or Poisson regression in our multivariable linear models. For Sub-aim 2.b we will examine how effectiveness of the interventions may vary by sex, age, and rurality using frequency tables and crossing outcome proportions by levels of sex, age, and rurality. Examination of interaction terms (sex by intervention, age by intervention, etc.) in multivariable models, as well as subset analysis as appropriate to illuminate such differences, will allow us to evaluate differences across these covariates in effectiveness of the intervention arms. For Sub-aim 2.c we will obtain an estimate of the sample quality under each of the three intervention conditions and also an estimate of the sample quality likely to result when these interventions are deployed to the larger population and compare those to national sample quality estimates (96%).

3 HUMAN SUBJECTS PROTECTION

3.1 RECRUITMENT AND INFORMED CONSENT

Quantitative Study: After obtaining Alaska Area Institutional Review Board (IRB) and appropriate Tribal review and clearance, a list of eligible patients will be drawn from each participating THOs electronic medical record (EMR) system. Each healthcare system in the ATHS uses comprehensive EMRs and administrative databases that will be used to collect contact information (e.g., phone number(s) and mailing address), demographic information (e.g., age, sex, and race and ethnicity), identify patients due for screening, provider orders, screening test completion, and pathology results. Prior history of CRC screening, including time since the last screening, will be retrospectively collected from EMRs. Current Procedural Terminology, Healthcare Common Procedure Coding System, and laboratory codes will be used to ascertain receipt of screening and screening method, regardless of indication. See Appendix A for list of variables to be collected. All variable data collected for this study will be stored in REDCap (Research Electronic Data Capture), a secure HIPAA compliant database system.

Communities will be randomized to one of two interventions: high intensity or medium intensity. The high intensity intervention will include navigated outreach, a mailed MT-sDNA kit, mailed culturally appropriate educational material describing CRC screening options available, and follow-up reminders (Study Group 1). The medium intensity intervention will include mailed culturally appropriate educational material describing CRC screening options available, including MT-sDNA, and navigated follow-up outreach reminders (Study Group 2). Participants will be recruited by mail and phone calls, depending on the intervention arm. All remaining communities in the region served by that THO will receive usual care and will not have direct outreach.

Patients who requested MT-sDNA for CRC screening, received a kit, but did not return it will be contacted to assess reasons for non-adherence. Survey data will be collected verbally by phone by an ANTHC study team member and stored in REDCap, a secure HIPAA compliant database system. This data will be stored with identifying information such as name and phone number, which is needed to contact patients for the phone survey but no personally identifying information will be included in the reporting of the non-adherence data analysis.

Waiver of Consent: As individuals will be selected for each trial arm based on their randomized community, we requested a waiver of informed consent for eligibility and group assignment from the Alaska Area IRB as well as the Alaska Native Tribal Health Consortium (ANTHC) and the ANTHC and SCF Privacy Officers, who have given approval for the waiver of consent. We will also request a waiver of informed consent from participating THOs prior to study implementation.

The rationale for the waiver of consent is that the study will randomize by community (cluster randomization) so that everyone who is eligible for CRC screening in that community will be offered the same intervention (or usual care). The disclosure of the study purpose as part of the consent process to individuals would bias the research so that the results will not be meaningful, since the study is trying to determine on a community level how much offering these different types of CRC screening interventions would help increase overall community screening rates. The purpose of the waiver of informed consent is to avoid potential selection/volunteer bias. Additionally, if participants are consented, they will know which intervention community they are in, and so there might be bias resulting from that as well. Patients who did not return their mt-sDNA kit for CRC screening and those that scheduled a colonoscopy but never completed it will be contacted for a phone survey and fall under this waiver of consent. These are patients who participated in the intervention and are being followed up with to assess why they chose to screen with mt-sDNA or colonoscopy, but ultimately did not return their kit or complete a procedure to complete screening.

To help address potential concerns raised by this type of study design, the regional THOs and their Privacy Officers will be asked to approve the waiver of consent prior to study implementation. Clinic staff (front desk, Community Health Aides, midlevel providers) in intervention communities will be

informed that a CRC outreach project is occurring in case they are contacted by community members but not which arm their community is in. Lastly, since the risks posed by this intervention do not exceed the threshold of minimal risk, an independent monitoring committee (Data and Safety Monitoring Committee; DSMC) is not required. However, to provide additional safeguards for this study, we will engage a DSMC to provide study oversight and consultation (see *3.3.2. Data and Safety Monitoring Plan)*.

Qualitative Study: We will recruit never or inadequately screened patients and Alaska tribal health system providers to participate in either focus groups (patients only) or key informant interviews (patients and providers) to identify barriers to receipt of CRC screening, as well as explore opportunities to increase screening using the MT-sDNA test. We will recruit Alaska Native patients who have not been screened or are not currently adherent to screening recommendations (colonoscopy within 10 years, sigmoidoscopy within five years, or FIT/FOBT within preceding 12 months) according to their tribal medical records at ANMC and at 1-2 participating regional THOs. Clinical staff will be recruited based on their involvement in the provision of CRC screening at the participating organizations.

Recruitment for focus groups will be conducted by Hays Research Group LLC to increase our chance of successfully recruiting the required number of AN people to participate in the focus groups. Hays Research Group LLC has extensive experience recruiting for and conducting health-related focus groups with AN people and has previously conducted focus groups for the EpiCenter and others within the ATHS. We will also use IRB- and tribally-approved study flyers and information sheets located at the Alaska Native Medical Center in Anchorage, AK and participating rural THOs to recruit for the study.

Upon recruitment, we will explain the purpose of the qualitative study to participants, and thoroughly review the consent with each participant individually (including for focus group participants). All focus group participants and key informants will sign an informed consent form that describes the focus group/interview, how the information that they provide will be used, and how their confidentiality will be protected. No names of participants will be associated with notes or transcriptions. We will have a translator available for those participants who have difficulty with the consent forms, or who would like further clarification in their Native language. Per Alaska Area IRB requirements, all consent forms and study documents will be written at grade 8 reading level or lower. All documents will be reviewed and approved by the IRB and necessary THOs.

There will be a short, anonymous questionnaire distributed before the focus group or interview to collect some general demographic information about the participants (age, gender, community). Focus groups will last approximately 2 hours and will be stratified by gender. Interviews are expected to take approximately 30-45 minutes of staff time. Focus groups may be completed using the Zoom platform which is a HIPAA compliant web and video conferencing platform. In this case, focus groups will still be recorded so they can be transcribed and participant names will be excluded from the transcripts. Focus group guides have been created for both in-person and virtual focus groups and the appropriate guide will be utilized depending on the method we use. The focus groups and interviews will be tape-recorded and the tapes transcribed by a private transcription service (temi.com) to ensure no voice recognition by the transcriber. The analysis, interpretation, and reporting will be done by EpiCenter staff trained in research and with current CITI certifications on file with the AAIRB. Qualitative computer software (ATLAS.ti) may be used for analysis as needed.

Focus group and interview participants will be given a thank you gift for their time. This will be a gift card, at a value to be determined in collaboration with our THO partners, and after approval from the Alaska Area IRB. In addition to gift certificates for focus group participants we will have $25 taxi cab and $25 childcare vouchers to help people be more readily able to participate in the focus groups. These will be offered to all in-person focus group participants in THO regions where we conduct in-person

focus groups. Our previous studies have provided $25 for interviews and $50 for focus group participation. We do not anticipate the need for additional retention strategies, as interviews and focus groups will be one-time, and will occur soon after recruitment (ideally <7 days).

3.2 POTENTIAL RISKS

We will collect information on CRC screening clinical care including in tribal electronic medical record (EMR), as well as data from the Alaska Native Tumor Registry (ANTR). There is a small risk of loss or accidental release of personally identifiable information during data extraction. Risk associated with this occurrence is expected to be minimal, as personally identifiable information will not be included in the study database. The research team will have access to personally identifiable information only for the purpose of medical chart review. The Alaska Native Health Campus is a Covered Entity; all electronic data will be stored in the secure, password-protected campus network system and only the study research team designated in the Alaska Area IRB-approved protocol have access to the data. Any paper recorded (e.g., informed consent documentation) will be stored in locked cabinets in the Alaska Native Epidemiology Center office. Access to this area is restricted to keycard holders only; only the PI and Study Coordinator will have direct access to this key.

It is possible that there may be the potential for stigmatization of or concern from the Alaska Native community regarding findings from the analyses. We believe the risk of this to be small, due to collaboration with and oversight by tribal review entities (see below).

As with all scientific studies, it is possible that we will not generate results that will have direct therapeutic or preventive benefit to Alaska Native people. This possibility is not likely to cause adverse effects.

3.3 PROTECTION AGAINST RISK

Every effort will be made to maintain the confidentiality of the participants' personal information. Files and computers are accessible only to the Study's research team. Care will be taken to ensure that information is collected and presented in such a way that individuals cannot be identified. For example, no personally identifiable information will be included in the study database used for analysis. The research team will have access to personally identifiable information only for the purpose of medical chart review to determine CRC screening completion and outcomes.

All research team members have been trained in HIPAA, confidentiality and medical record compliance standards, as appropriate. Furthermore, all ANTHC research staff sign a Confidentiality Statement as a condition of employment, which is reviewed annually and includes a clause indicating a break in confidentiality is grounds for immediate dismissal. All members of the research team have verification of Collaborative Institutional Training Initiative (CITI) human subject protections training. All investigators and staff members involved in the project will sign confidentiality and data use agreements to avoid misuse or accidental release of data. Access to research data will be strictly limited to study staff directly involved in data analysis and interpretation, under the direction of the PI and Study Coordinator.

Access to research data will be strictly limited to study staff directly involved in data analysis and interpretation, under the direction of the PI. Study staff will only be given access to the minimum necessary information to complete their assigned tasks. For example, the Research Assistant will have access to limited personally identifiable information for a limited period of time, in order to complete medical chart review as described above. Any data that is shared with investigators external to ANTHC will be shared only with completion of a signed ANTHC Data Use Agreement. Only aggregated, de-identified data will be shared with other consultants, and any other individuals who may assist in the data interpretation process (e.g., tribal health leaders, ANTHC Research Consultation Committee).

We will work closely with ANTHC and regional tribal researchers and review boards to ensure that all

results are presented in a culturally appropriate, respectful way. All dissemination materials will present data in aggregate or summary form and in no way will identify individual participants. This protocol, and all materials designed to disseminate information or results from this study, will undergo ANTHC and regional THO tribal review and clearance.

3.3.1. Storage and Coding of Data

ANTHC data files are managed, processed, and stored in a secure environment (e.g., lockable computer systems with passwords, firewall system in place, virus/malicious intruder protection) and by controlling access to digital files with encryption and/or password protection. Necessary data security and storage mechanisms will be used as required by applicable laws to protect personal health information as per ANTHC policy. Login permissions to the shared folder are managed by ANTHC IT Administrators or the designated Data Manager. The Data Manager will also be responsible for naming conventions, version control, folder structures, and data dictionaries (as needed). The Data Manager will assign each individual in the linked database with a unique study ID that will be associated with the participant's information. The study PI will be responsible for ensuring that all data are kept secure and that the data management plan is reviewed annually.

3.3.2. Data and Safety Monitoring Plan

This is no more than a minimum risk study with a CRC screening intervention. Because the risks posed by this intervention do not exceed the threshold of minimal risk, an independent monitoring committee (Data Safety Monitoring Committee; DSMC) is not required. However, to provide additional safeguards for this study with AN people, we will engage a DSMC to provide study oversight and consultation. The DSMC for this clinical trial will consist of three (3) experts who are independent of this protocol. Ms. Dana Diehl, Director of Wellness & Prevention at ANTHC will be asked to chair the DSMC. The other DSMC members who will be invited to participate will include Dr. Timothy Thomas, Director of Research and Clinical Services at ANTHC, and Dr. Steven Vindigni, clinical gastroenterologist at the Alaska Native Medical Center. Dr. Thomas oversees ANTHC's Research Department and is the PI for a clinical intervention trial currently underway at ANTHC. Dr. Vindigni is a clinical gastroenterologist at the Alaska Native Medical Center. A representative of the participating regional THOs will be invited to join the committee if they would like to be involved.

The DSMC will review data on such aspects as participant enrollment, site visits, study procedures, data quality, and other measures of adherence to protocol. The DSMC will review data and individual reports related to unanticipated problems and adverse (AEs) and serious adverse events (SAEs). They will provide recommendations to the PI regarding problems and safety concerns. They will provide periodic reports to the PI indicating whether they see any reasons for change and document all their actions. The data manager will prepare tables with data to be reviewed by the DSMC at least annually.

All reportable AE, SAE and unanticipated problems experienced by participants will be reported to the AAIRB in addition to any adverse or serious adverse events in compliance with their Adverse Event Reporting Policy requirements. Within 72 hours after a reportable AE, SAE or unanticipated problem has been reported by the participant, it will be graded by the PI, forwarded to the study's DSMC for review, and then will be submitted by the PI to the AAIRB. In addition, all cumulative reportable AE, SAE and unanticipated problems included in the DSMC reports will be submitted to the AAIRB in the PI's Annual Progress Reports.

3.4 POTENTIAL BENEFITS OF THE RESEARCH

Individuals whose data will be included in this research will not receive any direct benefit from their participation in the research study. However, there are several societal benefits to AN people:

1. The primary goal of this research is to understand whether the use of MT-sDNA, as well as high and medium intensity interventions, help increase CRC screening among Alaska Native people. The

results of this study may be incorporated into Alaska Tribal Health System policies and procedures and lead to more sustainable screening infrastructure and screening services access in the future.
2. This study will also identify barriers to CRC screening experienced by "never" and "rarely screened" Alaska Native people to identify additional strategies to increase screening in these groups, who have among the highest rates of CRC in the world. The benefit of this research is in our improved understanding of screening and access patterns, as well as potential improvements that can be made to the Alaska Tribal Health System to reduce this health disparity.
3. This research hopes to serve as an example of how to conduct research in a culturally appropriate and respectful manner, and will provide a basis for ongoing discussion around healthcare delivery research among AN people. Translational and healthcare delivery research is proving informative regarding best practices for care, including cancer, in other populations, yet has been underexplored for its potential to be informative regarding cancer prevention and control among AN people. Working closely with tribal stakeholders to develop and conduct this research, we hope to identify strategies and policies that can be implemented in the tribal health system to improve AN healthcare. Our goal is that by working with AN tribal health leaders and community members in this way, this study will join in other current cutting edge science being conducted at the AN Health Campus and pave the way for future research programs that could benefit the health of AN people.

3.5 DISPOSITION OF THE DATA

Per standard scientific practice, data will be retained, on a secure network drive within the ANTHC firewall, at the completion of the study. Per NIH data sharing policies, data may be made available to investigators for additional analyses beyond those proposed herein, given that all tribal and IRB processes are adhered to. Should additional analyses be considered as part of the existing project, an IRB modification will be submitted. Should external investigators wish to conduct additional secondary analyses on the linked database, they will apply to work in collaboration with existing study investigators, and a new protocol will be submitted for tribal and IRB review. Data will be retained by Study Investigators for a period of six years past the publication of the final manuscript resulting from this work. This period of time is to ensure that Study Investigators are able to answer any questions arising from the publication of results. The Study PI will be responsible for handling ClinicalTrials.gov requirements for this project. Study results will be reported within one year of final collection of data through ClinicalTrials.gov. Results information will include participant flow, demographic and baseline characteristics, outcomes and statistical analyses, adverse events, the protocol and statistical analysis plan, and administrative information.

3.6 PUBLICATION AND DISSEMINATION

The results generated by this research project will be shared across the ATHS in order to affect policy and systems change for AIAN people throughout Alaska. Our results will be interpreted in consultation with statewide and regional tribal health leaders, as well as the ANTHC Research Consultation Committee. Findings will be disseminated to members of the clinical community through forums such as Ground Rounds, which are broadcast statewide for attendees from our THO partners. Results will be shared with the wider community using culturally appropriate formats such as local and regional newspapers or radio interviews. All community dissemination materials will be developed at an appropriate level of health literacy, in collaboration with the ANTHC Research Consultation Committee.

We will share these results with the scientific community through a series of scientific publications and presentations at scientific meetings. All manuscripts, abstracts, and community dissemination materials resulting from this research will be approved by ANTHC and appropriate THOs before any publication or presentation.

APPENDIX A. POTENTIAL VARIABLES TO BE COLLECTED FROM THE MEDICAL RECORD

1. Contact Information
    a. Telephone number(s)
    b. Mailing address

2. Demographics:
    a. Gender
    b. Date of birth
    c. Race(s)
    d. Hispanic or Latino origin
    e. Town and state of residence
    f. County/census area

3. CRC Clinical Data Elements:
    a. History of CRC screening
    b. Personal history of CRC or polyps
    c. Family history of CRC
    d. Currently experiencing CRC symptoms (rectal bleeding, blood in stool, etc.)
    e. Test appointment date schedules, or fecal kit distributed
    f. Screening adherence (test performed, pending, not performed)
    g. Indication for test(s) (screening, surveillance, diagnostic)
    h. Type of test(s) performed (colonoscopy, flexible sigmoidoscopy, DCBE, etc.)
    i. Date of test(s)
    j. Result of test(s) clinical diagnosis
    k. Was a biopsy/polypectomy performed
    l. Was the bowel preparation adequate
    m. Was the cecum reached during colonoscopy
    n. Test(s) outcome complete
    o. Recommended follow-up procedure(s)
    p. Additional test(s) required? Type
    q. Histology of the most severe polyp/lesion
    r. Total number of adenomatous polyp/lesion
    s. Size of largest adenomatous polyp/lesion
    t. Histology from surgical resection
    u. Date surgery performed
    v. Status of final diagnosis
    w. Final diagnosis
    x. Date of final diagnosis
    y. Recommended next screening/surveillance test
    z. Indication for next test(s) (screening, surveillance)
    aa. Recommended time interval till next test
    bb. Recurrent cancers
    cc. Status and date of cancer treatment
    dd. Tumor Registry data: diagnosis, histological type, behavior, primary site, AJCC stage, tumor size, CS-derived SS2000

LITERATURE CITED

1. Carmack A, Schade, TL, Sallison, I, Provost EM, Kelly, JJ. *Cancer in Alaska Native People: 1969-2013, The 45 Year Report.* Anchorage, AK: Alaska Native Epidemiology Center, Alaska Native Tribal Health Consortium;2015.
2. Kelly JJ, Alberts SR, Sacco F, Lanier AP. Colorectal cancer in Alaska Native people, 2005-2009. *Gastrointest Cancer Res.* 2012;5(5):149-154.
3. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med.* 1993;328(19):1365-1371.
4. Selby JV, Friedman GD, Quesenberry CP, Jr., Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med.* 1992;326(10):653-657.
5. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet.*375(9726):1624-1633.
6. US Department of Health and Human Services. *Colorectal cancer screening prevalence data: Behavioral Risk Factor Surveillance System.* Atlanta, GA: Centers for Disease Control and Prevention;2016.
7. Indian Health Service. *Alaska Area Aggregate GPRA [Government Performance and Results Act of 1993] Clinical Performance Report, CRS [Clinical Reporting System], Version 18.0.* Anchorage, Alaska: Alaska Area Native Health Service;2017.
8. Yip R, Limburg PJ, Ahlquist DA, et al. Pervasive occult gastrointestinal bleeding in an Alaska native population with prevalent iron deficiency. Role of Helicobacter pylori gastritis. *JAMA.* 1997;277(14):1135-1139.
9. Parkinson AJ, Gold BD, Bulkow L, et al. High prevalence of Helicobacter pylori in the Alaska native population and association with low serum ferritin levels in young adults. *Clinical and diagnostic laboratory immunology.* 2000;7(6):885-888.
10. Redwood D, Provost E, Asay E, et al. Comparison of fecal occult blood tests for colorectal cancer screening in an Alaska Native population with high prevalence of Helicobacter pylori infection, 2008-2012. *Prev Chronic Dis.* 2014;11:E56.
11. Alaska Native Medical Center. *Colorectal Cancer Screening Guidelines.* Anchorage, AK: Alaska Native Tribal Health Consortium 2013.
12. Redwood D, Joseph DA, Christensen C, et al. Development of a flexible sigmoidoscopy training program for rural nurse practitioners and physician assistants to increase colorectal cancer screening among Alaska Native people. *J Health Care Poor Underserved.* 2009;20(4):1041-1048.
13. Redwood D, Provost E, Perdue D, Haverkamp D, Espey D. The last frontier: innovative efforts to reduce colorectal cancer disparities among the remote Alaska Native population. *Gastrointest Endosc.* 2012;75(3):474-480.
14. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet.* 2010;375(9726):1624-1633.
15. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med.* 2012;366(25):2345-2357.
16. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med.* 2009;150(1):1-8.
17. Brenner H, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. *J Natl Cancer Inst.* 2010;102(2):89-95.

18. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med.* 2013;369(12):1095-1105.
19. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. *Gastroenterology.* 2005;129(2):422-428.
20. Ahlquist DA, Wieand HS, Moertel CG, et al. Accuracy of fecal occult blood screening for colorectal neoplasia. A prospective study using Hemoccult and HemoQuant tests. *JAMA.* 1993;269(10):1262-1267.
21. Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology.* 2010;139(4):1128-1137.
22. U. S. Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2016.
23. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med.* 2014;370(14):1287-1297.
24. Heigh RI, Yab TC, Taylor WR, et al. Detection of colorectal serrated polyps by stool DNA testing: comparison with fecal immunochemical testing for occult blood (FIT). *PLoS One.* 2014;9(1):e85659.
25. Prince M, Lester L, Chiniwala R, Berger B. Multitarget stool DNA tests increases colorectal cancer screening among previously noncompliant Medicare patients. *World J Gastroenterol.* 2017;23(3):464-471.
26. Berger BM, Schroy PC, 3rd, Rosenberg JL, et al. Colorectal cancer screening using stool DNA analysis in clinical practice: early clinical experience with respect to patient acceptance and colonoscopic follow-up of abnormal tests. *Clin Colorectal Cancer.* 2006;5(5):338-343.
27. Johnson DH, Kisiel JB, Burger KN, et al. Multitarget stool DNA test: clinical performance and impact on yield and quality of colonoscopy for colorectal cancer screening. *Gastrointest Endosc.* 2017;85(3):657-665 e651.
28. Glanz K, Rimer BK, Lewis FM. *Health Behavior and Health Education: Theory, Research, and Practice.* 4th ed. San Francisco, CA: Jossey-Bass; 2008.
29. Weinstein ND. Testing four competing theories of health-protective behavior. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 1993;12(4):324-333.
30. Weiner BJ, Lewis CC, Stanick C, et al. Psychometric assessment of three newly developed implementation outcome measures. *Implement Sci.* 2017;12(1):108.
31. National Colorectal Cancer Roundtable, American Cancer Society. Meeting Report: Increasing Colorectal Cancer Screening for American Indians and Alaska Natives 2017; http://nccrt.org/wp-content/uploads/AIAN-CRC-Post-Summit-Report-11-28-2017-Final.pdf.
32. Doubeni CA, Fedewa SA, Levin TR, et al. Modifiable Failures in the Colorectal Cancer Screening Process and Their Association With Risk of Death. *Gastroenterology.* 2019;156(1):63-74 e66.
33. Redwood D, Provost E, Lopez ED, et al. A process evaluation of the Alaska Native Colorectal Cancer Family Outreach Program. *Health Educ Behav.* 2016;43(1):35-42.
34. Seeff LC, Major A, Townsend JS, et al. Comprehensive cancer control programs and coalitions: partnering to launch successful colorectal cancer screening initiatives. *Cancer Causes Control.* 2010;21(12):2023-2031.
35. Donaldson EA, Holtgrave DR, Duffin RA, Feltner F, Funderburk W, Freeman HP. Patient navigation for breast and colorectal cancer in 3 community hospital settings: an economic evaluation. *Cancer.* 2012;118(19):4851-4859.

36. Freeman HP. The origin, evolution, and principles of patient navigation. *Cancer Epidemiol Biomarkers Prev.* 2012;21(10):1614-1617.
37. Centers for Disease Control and Prevention National Center for Health Marketing (NCHM) Community Guide Branch. The Guide to Community Preventive Services. Cancer Prevention and Control: Increasing breast, cervical, and colorectal cancer screening http://www.thecommunityguide.org/cancer/index.html. Accessed 4/11/2019.
38. Community Preventive Services Task F. Updated recommendations for client- and provider-oriented interventions to increase breast, cervical, and colorectal cancer screening. *Am J Prev Med.* 2012;43(1):92-96.
39. Allen JD, Barlow WE, Duncan RP, et al. NIH State-of-the-Science Conference Statement: Enhancing Use and Quality of Colorectal Cancer Screening. *NIH Consens State Sci Statements.* 2010;27(1).
40. Beydoun HA, Beydoun MA. Predictors of colorectal cancer screening behaviors among average-risk older adults in the United States. *Cancer Causes Control.* 2008;19(4):339-359.
41. Wilkins T, Gillies RA, Harbuck S, Garren J, Looney SW, Schade RR. Racial disparities and barriers to colorectal cancer screening in rural areas. *J Am Board Fam Med.* 2012;25(3):308-317.
42. Coughlin SS, Thompson T. Physician recommendation for colorectal cancer screening by race, ethnicity, and health insurance status among men and women in the United States, 2000. *Health Promot Pract.* 2005;6(4):369-378.
43. Klabunde CN, Vernon SW, Nadel MR, Breen N, Seeff LC, Brown ML. Barriers to colorectal cancer screening: a comparison of reports from primary care physicians and average-risk adults. *Med Care.* 2005;43(9):939-944.
44. Wee CC, McCarthy EP, Phillips RS. Factors associated with colon cancer screening: the role of patient factors and physician counseling. *Prev Med.* 2005;41(1):23-29.
45. Jones RM, Woolf SH, Cunningham TD, et al. The relative importance of patient-reported barriers to colorectal cancer screening. *Am J Prev Med.* 2010;38(5):499-507.
46. Anderson JC, Fortinsky RH, Kleppinger A, Merz-Beyus AB, Huntington CG, 3rd, Lagarde S. Predictors of compliance with free endoscopic colorectal cancer screening in uninsured adults. *J Gen Intern Med.* 2011;26(8):875-880.
47. Filippi MK, Braiuca S, Cully L, et al. American Indian Perceptions of Colorectal Cancer Screening: Viewpoints from Adults Under Age 50. *J Cancer Educ.* 2012.
48. Daley CM, James AS, Filippi M, et al. American Indian Community Leader and Provider Views of Needs and Barriers to Colorectal Cancer Screening. *Journal of health disparities research and practice.* 2012;5(2).
49. Kahneman D. *Thinking, fast and slow.* New York: Farrar, Straus and Giroux; 2011.
50. Thaler R. *Misbehaving: the making of behavioral economics.* W. W. Norton & Company; 2015.
51. Centers for Disease Control and Prevention, Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion. Colorectal Cancer Control Program (CRCCP) Social Ecological Model. 2011; http://www.cdc.gov/cancer/crccp/sem.htm.
52. McLeroy KR, Bibeau D, Steckler A, Glanz K. An ecological perspective on health promotion programs. *Health Educ Q.* 1988;15(4):351-377.
53. Redwood D, Provost E, Asay E, Ferguson J, Muller J. Giant inflatable colon and community knowledge, intention, and social support for colorectal cancer screening. *Prev Chronic Dis.* 2013;10:E40.
54. Burnett-Hartman AN, Mehta SJ, Zheng Y, et al. Racial/Ethnic Disparities in Colorectal Cancer Screening Across Healthcare Systems. *Am J Prev Med.* 2016;51(4):e107-115.

55. Codori AM, Petersen GM, Miglioretti DL, Boyd P. Health beliefs and endoscopic screening for colorectal cancer: potential for cancer prevention. *Preventive medicine.* 2001;33(2 Pt 1):128-136.
56. Tariq S, Woodman J. Using mixed methods in health research. *JRSM short reports.* 2013;4(6):2042533313479197.
57. Ivankova NV, Creswell JW, Stick SL. Using mixed-methods sequential explanatory design: from theory to practice. *Field Methods.* 2006;18:3-20.
58. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health.* 1999;89(9):1322-1327.
59. Norton Sound Health Corporation. Reducing Childhood Hearing Loss in an Alaska Native Population Through a New School Screening and Referral Process That Utilizes Mobile Health and Telemedicine (ClinicalTrials.gov Identifier: NCT03309553). https://clinicaltrials.gov/ct2/show/NCT03309553, 2019.
60. Eldridge SM, Ukoumunne OC, Carlin JB. The intra-cluster correlation coefficient in cluster randomized trials: A review of definitions. *International Statistical Review.* 2009;77(3):378-394.