Examples of Funded Grants in Healthcare Delivery Research

Overview
The National Cancer Institute (NCI) frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let the Healthcare Delivery Research Program (HDRP) post excerpts of their healthcare delivery research grant applications online.

About
We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. We only include a copy of the SF 424 R&R Face Page, Project Summary/Abstract (Description), Project Narrative, Specific Aims, and Research Strategy; we do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., performance sites, key personnel, biographical sketches). To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application).

Accessibility
Individuals using assistive technology (e.g., screen reader, Braille reader) who experience difficulty accessing any information should send an email to the Healthcare Delivery Research Program (NCIHDRP@mail.nih.gov).

424 R&R and PHS-398 Specific
Table Of Contents

SF 424 R&R Face Page

PI: CORONADO, GLORIA D

Grant Number: 1 R01 CA218923-01A1

Title: Prediciting and addressing colonoscopy non-adherence in community settings

FOA: PA16-160

FOA Title: NIH Research Project Grant (Parent R01)

Organization: KAISER FOUNDATION RESEARCH INSTITUTE

Department: Center for Health Research NW

Senior/Key Personnel: Gloria Coronado PhD

Organization: Kaiser Foundation Hospitals

Role Category: PD/PI

Project Summary/Abstract

Colorectal cancer is the second-leading cause of cancer death in the U.S. While research has shown that colorectal cancer screening decreases colorectal cancer incidence and mortality, only 65% of eligible adults were screened at the recommended interval in 2015. Even more troubling, those who are screened do not always get timely follow-up care for abnormal results. Dr. Lynn Butterly demonstrated that patient navigation can effectively raise rates of colonoscopy uptake among low-income, uninsured patients in New Hampshire, boosting rates 27 percentage points over usual care (96.2% vs 69.3%, P<.001). Using data from the STOP CRC study of 26 community clinics, our team developed a risk prediction model that can stratify patients according to their probability of adherence with follow-up colonoscopy. Our study will answer a key pragmatic question: can patient navigation effectively improve follow-up colonoscopy among patients who have a moderate or low probability of adhering to follow-up colonoscopy; and secondarily, does the effectiveness of patient navigation differ by patients' probability level?

We will build on our successful ongoing research to test a patient-level intervention, driven by the Chronic Care Model, to increase diagnostic follow-up for colorectal cancer screening. In Aim 1, we will validate the risk prediction model, stratify patients according to risk, and adapt patient navigation materials to local resources and settings. In Aim 2, we will conduct a two-arm randomized-controlled trial involving 28 clinics (~1200 patients with positive fecal tests) and will compare patient navigation and usual care in raising rates of follow-up colonoscopy. We will assess the effectiveness (completion of colonoscopy within 1 year) of the program overall, as well as the effectiveness by category of probability of adherence to follow-up colonoscopy (moderate vs. low). This large-scale, clinic-randomized, two-arm follow-up colonoscopy program among safety net patients will leverage the expertise of our research team, which has implemented numerous systems-based interventions in multiple health care settings and used electronic health record tools to deliver clinic-based interventions. We will build on these successes in undertaking the largest study to-date addressing follow-up colonoscopy uptake among patients who receive care in safety net clinics. This study could optimize the delivery of patient navigation, support the broad adoption of patient navigation programs, and greatly improve colonoscopy follow-up rates in this vulnerable population.

Project Narrative

Thousands of adults each year undergo screening for colorectal cancer through a fecal test, but those whose test results are positive do not always get timely follow-up colonoscopies. Our team has developed a model that can tell which patients are likely to get a follow-up colonoscopy, and we will use the model to test whether patient navigation can increase follow-up colonoscopy among patients who have a moderate or low probability of getting follow-up. Our goal is to catch and treat colorectal cancer earlier.

Specific Aims

Of the 8.7 million adults who complete fecal testing in the US each year, about 481,000 will have a positive test result and need a colonoscopy. Many of these people, however, forgo follow-up colonoscopy even though patients who screen positive on fecal testing have a 1 in 20 chance of having colon cancer. This is especially troubling as delays in follow-up colonoscopy of 1 year lead to a 16% increased mortality and 10% reductions in life-years gained from screening.

Patient navigation is increasingly being used to address health care needs of the medically underserved. Patient navigation has boosted rates of colorectal cancer (CRC) screening and follow-up in several previous reports, with effect sizes ranging from 11–28%. In a New Hampshire-based program, for example, Dr. Lynn Butterly demonstrated that patient navigation can effectively raise rates of colonoscopy uptake among low- income, uninsured patients, boosting rates 27 percentage points over usual care (96.2% vs 69.3%, P<.001). In this program, however, 69% of usual care patients got a colonoscopy— that is, they did not need patient navigation. Despite these results, previous research has revealed little about the effectiveness of patient navigation among patients who need it most.

If health systems could determine which patients were likely to forgo colonoscopy, they could funnel their education and outreach efforts, including navigation efforts, to these patients. Knowing which patients could benefit from patient navigation could optimize the delivery of these services, address health disparities, reduce associated costs, and support broad adoption of patient navigation programs. The Predicting and Addressing Colonoscopy in Safety Net Settings (PRECISE) will assess the risk of colonoscopy non-adherence among patients with a positive fecal test, and test patient navigation as an approach to improve colonoscopy adherence among patients who need it.

Risk prediction models offer a powerful tool for further improving CRC outcomes. These models have the potential to improve care quality and reduce health care costs, but more evidence is needed. Our team has developed a risk-prediction model using data from a large pragmatic study involving 26 community health center clinics (STOP CRC). This proposal will answer a critical pragmatic question: Is patient navigation an effective intervention for patients who have a high or moderate risk of forgoing colonoscopy? And secondarily, does the effectiveness differ by risk level?

Our prospective cohort study will evaluate the effectiveness of patient navigation in CHC settings. We will collaborate with our advisory board, composed of key clinicians and patients, researchers, and policymakers, to establish a procedure to conduct and evaluate a patient navigation program that aims to increase rates of follow-up colonoscopy among diverse patient populations served by safety net clinics. Phase 1 (Aim 1) will be a milestone-driven planning process in which we will validate our risk prediction model and apply our risk prediction model to stratify the patients and adapt patient navigation materials for the local context. Phase II (Aims 2-3) will be a large-scale, patient randomized-controlled trial that will include 1080 patients at a large 34- clinic community heath center in Washington State. Our study, **Predicting and addressing colonoscopy non-adherence in community settings (PRECISE),** will fulfill the following aims:

Specific Aim 1: Validate externally the predictive risk score using Sea Mar CHC's robust data including 29,000 patients age-eligible for colorectal cancer screening; stratify patients according to risk of non-adherence to follow-up colonoscopy; and adapt patient navigation program for our local context.

Specific Aim 2: Assess the effectiveness, costs, and cost-effectiveness of a centralized, phone-based patient navigation program for follow-up colonoscopy receipt for patients at moderate risk or high risk for non- adherence.

Specific Aim 3: Assess differences in the intervention arms in secondary outcomes (e.g. time to colonoscopy receipt, no-show/canceled appointments, colonoscopy quality) and moderators of intervention effectiveness (e.g. probability level, intervention dose, and patient age, ethnicity, and sex).

The proposed research will drive the adoption of patient navigation programs that are precisely delivered to those who need them the most. These programs will optimize health care resources and address persistent health disparities associated with receipt of follow-up to abnormal cancer screening tests. Our findings will have the capability of being generalized to other health systems and of being used to address multiple health issues for which patient navigation can offer promise. Knowing which patients could benefit from patient navigation could optimize the delivery of such services, address health disparities, and support broad adoption of patient navigation programs.

3. Research Strategy

A. Significance

Many patients with positive fecal tests forgo colonoscopies. Of the 8.7 million adults who will complete fecal testing for colorectal cancer (CRC) in the US this year,[9] about 481,000 will have a positive test result that requires a follow-up colonoscopy.[9] Many of these people, however, forgo follow-up colonoscopy even though patients who screen positive on fecal testing have a 1-in-20 chance of having CRC. This is concerning as delays in follow-up colonoscopy lead to increased mortality. Data from Kaiser Permanente Northern California show that individuals who received colonoscopies 12 months after a positive result from a fecal test had a 4% higher incidence and 16% higher mortality from the disease than individuals who received a colonoscopy within 2 weeks.[10] The human cost of this "missed opportunity" is tremendous and analyses show those who delayed screening for a year lost nearly 10% in life-years compared to those with prompt follow-up.[10]

Colonoscopy follow-up rates vary across populations. We know that rates of follow-up colonoscopy vary by health care setting, ranging from 42-59% in Veterans Administration facilities[11-14] to 81-82% in integrated care settings.[15,16] While evaluations in community health centers (CHCs) are rare, Liss and colleagues reported a 52% 1-year follow-up colonoscopy rate in a CHC study.[17] Similarly, our team observed a 54% 1-year follow-up rate in our STOP CRC project involving >50,000 patients in 26 CHC clinics [NIH UH3AT007782].[18] STOP CRC data further show troubling disparities in follow-up by race/ethnicity, with Hispanics following up at a lower rate than non-Hispanic whites (45% vs. 70%, within 18 months).[18]

Colonoscopy follow-up rates in community health centers are suboptimal. CHCs are community-governed centers providing comprehensive health services to a growing number of patients with complex health needs.[19] From 2008 to 2015, the number of CHCs increased by 27% and patients served in these centers increased by 42%. By 2016, CHCs served more than 24 million patients at 8,147 delivery sites across the US.[20] These centers face unique barriers to enrolling patients in specialty care, such as varied coverage rules among health plans and limited numbers of in-network gastroenterology (GI) providers. CHC patients often need scheduling support or help finding transportation to get to and from a colonoscopy appointment. GI facilities may have limited interpretive services and face other logistical issues in providing services to CHC patients. Krok-Shoen and colleagues,[21] for example, showed that CHC patients had a significantly lower 1-year rate of resolution of an abnormal cancer screening tests (breast, cervical, and colorectal cancers; median = 192 days) than did patients in academic medical centers (median = 161 days; P=0.004). These data illustrate a critical need for interventions to improve follow-up colonoscopy rates in these clinics. The proposed research will partner with a large CHC network to deliver a targeted intervention to improve follow-up colonoscopy rates.

Patient navigation is a promising approach to increase follow-up rates. Patient navigation is increasingly being used to address the health care needs of the medically underserved. Indeed, the National Colorectal Cancer Roundtable strongly endorses patient navigation for colonoscopy screening and follow-up.[22] Dr. Lynn Butterly demonstrated that patient navigation can effectively raise rates of colonoscopy uptake among low-income, uninsured patients in New Hampshire, boosting rates 27 percentage points over usual care (96.2% vs. 69.3%, P<.001).[23] Despite this promising research, almost all available studies have focused on *initial* CRC screening, rather than *follow-up* colonoscopy. A few small studies (the largest of which included 235 patients) indicate that patient navigation shows promise for follow-up colonoscopy as well.[3,4] Despite these results, previous research tells us little about the effectiveness of patient navigation for patients who need it most.

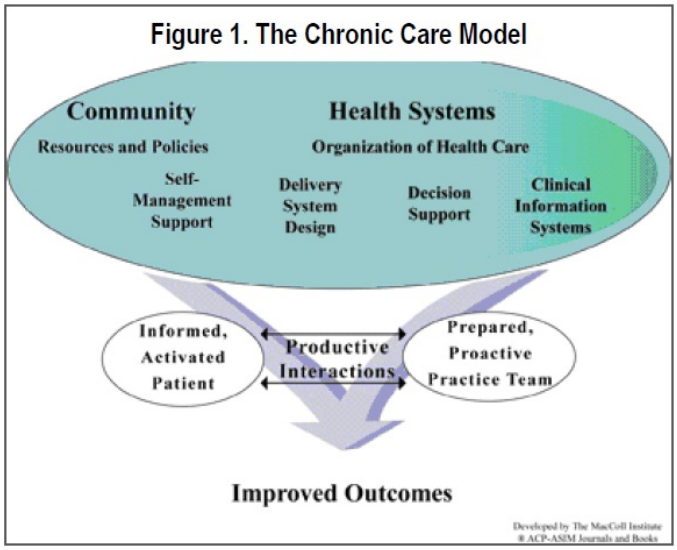
Despite promise, more information is needed to best target patient navigation resources. As noted above, published rates of follow-up colonoscopy range from 42-82%.[11-17] The successful New Hampshire program, for example, reported that a high proportion (69%) of non-navigated patients obtained a colonoscopy—that is, they did not need navigation. This finding is important because patient navigation programs can require extensive resources to adopt; previous cost evaluations of patient navigation have reported costs ranging from $50 to $332 per participant.[24-26] If health systems were able to determine which patients were likely to forgo colonoscopy, they could funnel their education and outreach efforts, including navigation efforts, into the individuals who need them most. Knowing which patients could benefit from navigation could optimize the delivery of such services, address health disparities, and reduce associated costs. The proposed research, Predicting and Addressing Colonoscopy in Safety Net Settings (PRECISE), will do just this by estimating the probability of colonoscopy adherence among patients with a positive fecal test,

and test patient navigation as an approach to improve colonoscopy adherence among patients who need it. Our study will also assess the cost of patient navigation. Of the prior studies on this topic,[24-26] only two have reported costs per follow-up to an abnormal cancer screening test. As such, data that evaluate the costs alongside the clinical outcomes of patient navigation are sorely needed.[24,27] To date, no study has reported the cost of navigation across patient groups defined by probability of adherence, as we propose.

Risk-prediction models can improve care quality and optimize health care resources, but more evidence is needed.[28] Electronic health record (EHR) data provide an unprecedented opportunity to identify patients at high risk of an event so that care can be personalized.[29] Personalized care delivered to those most likely to benefit is supported by national organizations, including the Institute for Healthcare Improvement.[30] While risk-prediction models hold promise for identifying patients who are likely to forgo colonoscopy, previous research on this topic is scarce. While Percac-Lima and Blumenthal and colleagues both developed scores to identify patients unlikely to obtain a colonoscopy, these models were based on academic primary care networks and integrated care systems, where rates of colonoscopy are higher than in CHCs and providers have easier access to data elements for the models.[31,32] As a result, these scores are not generalizable to CHCs, in which fewer data elements are available. Moreover, their scores identified patients at risk for not completing *initial* cancer screening, rather than *follow-up to an abnormal cancer screening result*. As such, we do not know whether this scoring system would generalize. Our team has developed a risk-prediction model specifically for follow-up colonoscopy receipt that relied on data from the STOP CRC trial of 26 CHC clinics.

Systems-based approaches are needed. Solving important public health issues such as disparities in CRC screening and follow-up is complex and depends on factors at multiple levels: individual, clinician and clinic, organizational, community, and societal. We will use the Chronic Care Model (CCM) (Figure 1) developed by Wagner and others[33] to identify these factors. The model specifies that optimization and integration of six components— evidence-based decision support, clinical information systems, delivery system redesign, health care organization, self-management support, and community resources—lead to positive interactions between patients and practice teams and to improved care outcomes. The CCM has been implemented in multiple settings and has led to improved outcomes[34] and reduced health care costs.[35-38] Our application of the CCM will emphasize evidence-based decision support and clinical information systems (via the deployment of the risk-prediction score) and health care organizations and community resources (via the testing of a patient navigation intervention).

Figure 1. The Chronic Care Model



Premise and importance. CRC claimed the lives of an estimated 52,000 adults in the US in 2016.[12,3] Improving screening and appropriate follow-up could reduce CRC mortality by more than 50% by 2020, representing over 27,000 lives saved.[4] These mortality reductions can only be achieved if patients receive appropriate follow-up to positive fecal test results.[39,40] Only an estimated 54% of patients who get care in CHCs receive a follow-up colonoscopy within a year of a positive fecal test result;[17] that is, the benefits of fecal testing are nullified for 46%. While patient navigation is widely endorsed as an effective approach to prompt receipt of cancer screening and follow-up care, previous evaluations have included patients who are likely to undergo screening or follow-up without any intervention. PRECISE will use EHR data to direct patient navigation resources to patients who need it the most. PRECISE will allow clinics to deliver immediate navigation, when patients are most easily reached and before their cancers advance to a more lethal stage. We will also conduct an economic analysis to inform health system decision-making regarding adoption of a risk model approach to targeting patient navigation resources. Our study will be 4 times larger than any previous evaluation of patient navigation for *follow-up* colonoscopy. If effective, PRECISE will facilitate the broad adoption of precision patient navigation programs and promote Institute of Medicine directives to deliver the right intervention to the right patient at the right time.

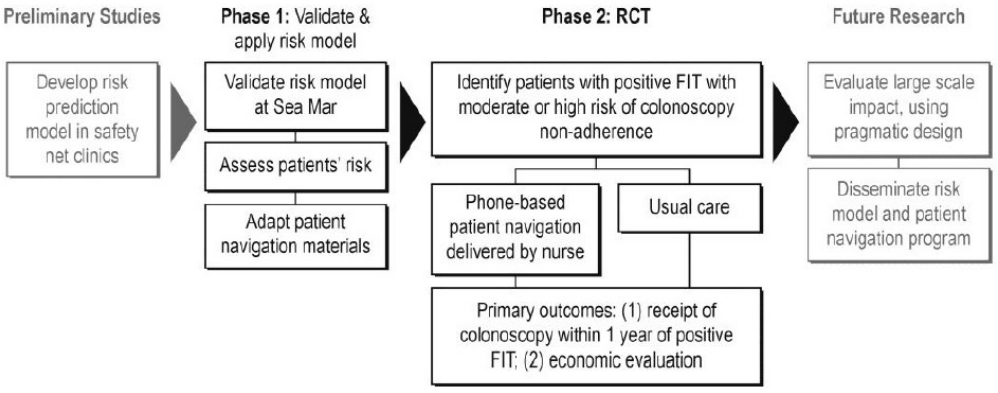
B. Innovation

- Our study will be the first to answer the key precision medicine question: how effective is patient navigation among patients who have a moderate or low probability of adhering to follow-up colonoscopy recommendations?
- While some risk-prediction models have been used to identify patients who are likely to forgo cancer screening, no previous investigation has tested the effectiveness of patient navigation in subgroups based on their probability of adherence to follow-up recommendations.
- We will conduct an economic evaluation of patient navigation across patient subgroups defined by their probability of colonoscopy adherence. No study has adequately addressed patients at different risk levels to assess corresponding differences in value for money.
- Our program will rely on trained clinic staff and be embedded into clinic workflows. In contrast, most previous patient navigation evaluations have relied on research staff to deliver programs to a subset of consented research participants.

C. Approach

C.1. Overview. This study will increase follow-up colonoscopy rates in large numbers of diverse patients by testing a patient navigation program among patients at moderate or low probability of obtaining follow-up colonoscopy. **Phase I** (Aim 1) will be a milestone-driven planning phase to externally validate the risk-prediction score, stratify patients' probability of adhering to follow-up colonoscopy, and adapt patient navigation materials for the local context (Figure 2). **Phase II** (Aims 2–3) will be a large-scale, targeted, patient-randomized controlled trial that will include ~1200 patients across 28 clinics in western Washington State. A central advisory group of key clinicians and patients, researchers, and policy-makers will guide the study implementation, results interpretation, and dissemination. We will work with our Advisory Board to compare rates of follow-up colonoscopy completion in ~900 patients with a moderate or low risk of colonoscopy adherence who are randomized to receive either a telephone-based program of patient navigation delivered by trained clinical staff (developed by Dr. Lynn Butterly and replicated by Dr. Peggy Hannon, project consultant) or usual care. We will also assess the cost of the program for patient groups defined by risk level (moderate or low risk of adhering to follow-up colonoscopy). Secondarily, we will assess differences in process outcomes and explore possible moderators of effectiveness. Results of this research could lead to large-scale testing and adoption of targeted patient navigation approaches in clinical settings.

Figure 2. Study Activities



C.2. Research team and preliminary studies. Our multidisciplinary research team includes investigators with a record of developing and testing multiple cancer prevention interventions; analysts with years of experience designing interventions to improve cancer screening and follow-up care rates in multiple settings; and implementation scientists and qualitative researchers who can expand the real-world applicability of our findings. Dr. Coronado will lead this project in partnership with Dr. Ricardo Jimenez, medical director of Sea Mar Community Health Centers. This project builds upon an existing partnership with Dr. Peggy Hannon, who is leading the replication of the New Hampshire Colorectal Cancer Screening Program (NHCRCSP), and Mr. Boxberger, who offers expertise in health information technology in safety net clinics and will manage the installation of the risk-prediction model at Sea Mar Community Health Centers. The project will be supported by two GIs, a currently practicing GI at Kaiser Permanente Northwest (Dr. Mummadi, Co-I) and a retired GI (Dr. Wilborn, consultant), who served as a member of the Data Safety Monitoring Board of STOP CRC. All investigators have a long and successful history of collaboration; Drs. Johnson, Smith and Coronado collaborated over the past year to develop the risk-prediction model (with input from Dr. Mummadi). Drs. Smith and Leo serve as Co-Investigators on an ongoing NIH-funded study led by Dr. Coronado [U01MD010665].

Preliminary Study #1: STOP CRC (NIH 4UH3CA188640-02; PIs: Coronado, Green; Co-I: J. Schneider) is a cluster-randomized comparative-effectiveness pragmatic trial of CRC screening involving eight CHCs (26 clinics; ~50,000 patients) randomized to control and intervention arms. The intervention uses an EHR-embedded program to identify patients who are overdue for CRC screening and mail fecal test kits to them (all clinics are using fecal immunochemical test [FIT] kits). Over 15,000 patients have been mailed FIT kits. **Pilot data show that the program increased FIT testing by 38 percentage points.**[41]

Our team conducted chart abstraction of 613 charts of patients who had positive fecal test results. Findings showed that 87% of patients were referred and 54% received a colonoscopy within 1 year. Among patients who were referred but did not receive a colonoscopy, the most common EHR-documented reasons were that the patient declined (28%), could not be contacted (11%), or had a prior recent colonoscopy (8%). No reason was found for nearly half of the patients (44%) (Table 1).

Table 1. EHR-Documented Reasons for No Referral or Colonoscopy, in STOP CRC clinics (n = 613)*

Reason	Not Referred (n = 84) N (%)	Referred, No Colonoscopy (n = 195) N (%)
No reason indicated	26 (32.1)	86 (44.1)
Patient declined	24 (29.6)	54 (27.7)
Unable to contact	4 (5.0)	21 (10.8)
Recent colonoscopy	22 (25.9)	25 (12.8)
Other	5 (5.9)	9 (7.7)

*based on chart abstraction of 613 patients w/positive Fit results

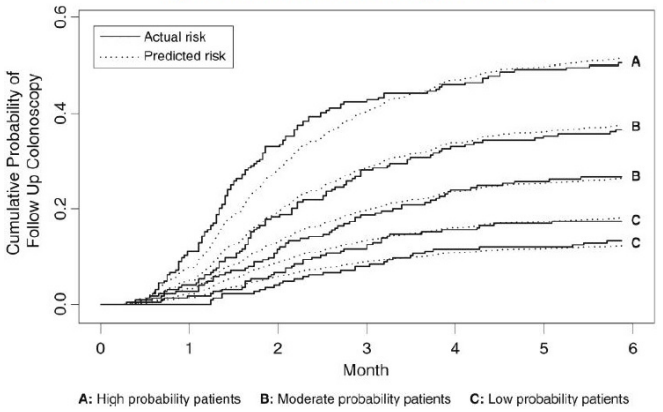
As part of STOP CRC, we conducted 15 qualitative interviews with GI providers and referral coordinators. Interviews identified multiple barriers to follow-up colonoscopy (Table 2). These barriers included issues with bowel preparation; logistical issues, such as with arranging a ride or taking time off work; insurance and cost-related barriers; and fear of undergoing the exam. The team conducted additional qualitative interviews with patients who did not get a follow-up colonoscopy after an abnormal fecal test result; some patients did not know why they needed a colonoscopy and others faced fear and financial barriers to completing the test (unpublished data). Through this and related studies, the research team has established key relationships with a network of community clinics and uncovered patient- and system-level factors critical to increasing rates of follow-up colonoscopy in underserved populations that will be invaluable in the proposed study.

Table 2. Barriers to CRC Follow-up: Perspectives from Providers (n = 15) and Patients (n = 10)

Bowel preparation challenges	Providers	Patients
Bowel prep	√	
Logistical issues		
Arranging a ride	√	√
Unable to take time off work	√	√
Delays in getting appointment		√
Insurance/cost-related barriers		
Billing / insurance issues	√	
Cost of colonoscopy	√	√
Psychosocial/other issues		
Patient fears	√	
Confusion about colonoscopy	√	√
Multiple health issues		√

Preliminary Study #2: Predicting the need for navigation services for follow-up colonoscopy (KP Pilot funds; PI: Coronado; Co-Is: E. Johnson, D. Smith) is a pilot project to develop a risk-prediction model using data from STOP CRC clinics (1,122 patients with a positive FIT result and 1 year of follow-up data). Our team developed a prediction model using Cox regression. The model includes eight variables: age, Hispanic ethnicity, body mass index, number of clinic visits in the past year, frequency of missed clinic appointments, previous CRC screening, receipt of a flu vaccine in the past year, and clinic site. The model shows adequate separation of patients across probabilities of adherence to follow-up colonoscopy (bootstrap-corrected c-statistic = 0.65) and excellent calibration (high agreement between observed and predicted risk [Figure 3]). This c-statistic is considered adequate for our primary goal of directing patient navigation resources to those most likely to benefit. We used extrapolated data to account for the difference in follow-up colonoscopy receipt using chart-abstracted data (54%) and EHR codes (43%). Likelihood of obtaining a follow-up colonoscopy within 6 months varied across quintiles. While patients with the lowest predicted probability of adherence (bottom quintile) had a 25%

Figure 3. Cumulative Probability of Follow-Up



A: High probability patients **B:** Moderate probability patients **C:** Low probability patients

chance of obtaining a colonoscopy, patients with the highest predicted probability of adherence (top quintile) had a 93% chance of obtaining a follow-up colonoscopy. Our findings were unchanged when we extended the follow-up interval to 9 months. These findings demonstrate our successful preliminary research and our ability to develop a risk-prediction model using data from a large network of CHCs. This preliminary research will serve as the basis for our proposed research; that is, testing the effectiveness of a targeted patient navigation intervention among patients with a moderate or low probability of adherence, and secondarily testing the relative effectiveness and cost-effectiveness of patient navigation across probability groups (moderate- and low-probability levels).

C.3. Participating health centers. The proposed project is a partnership with Sea Mar Community Health Centers. Sea Mar operates 34 medical clinics (28 clinics will participate in this trial; non-participating clinics are specialty sites) and serves a patient population of ~250,000; ~29,000 are eligible for CRC screening. The proportion of Latino patients is 37%. Clinic personnel are sensitive to, and reflective of, the diverse populations they serve. Sea Mar has a fully integrated EHR platform tailored for primary care (Allscripts, Chicago, Illinois). Sea Mar has participated in efforts to raise its CRC screening rates by using a direct-mail FIT approach followed by automated and live reminders. As part of this effort, Sea Mar staff review ("scrub") the medical records of patients who are due for CRC screening and eliminate those with a recent prior colonoscopy. Thus, we estimate that the proportion of referred patients who are ineligible for colonoscopy to be relatively small. The estimates in Table 3 are based on current fecal testing rates (overall: 45%). The average number of patients per year with a positive fecal test result is 1,186; the average Sea Mar FIT positivity rate is 9%.

Table 3. Sea Mar Community Health Center Colorectal Screening Characteristics, July 1, 2016 – June 1, 2017

Health Center	Clinics (N)	Patients eligible for screening[1] (N)	Completed FIT in past year (%)	FIT results positive[2] (N)	High probability of adherence[3] (N)	Moderate/low probability of adherence[4] (N)
Sea Mar Community Health Center	28	29,281	45.0	1,186	237	949

[1] Patients aged 50 – 74; [2] positivity rate = 9%; [3] high probability of adherence = 20%; [4] moderate probability = 40%; low probability = 40%.

Dr. Coronado has a long-standing research partnership with Sea Mar, having led two NIH-funded studies in partnership with Sea Mar (5U54CA153502 and STOP CRC). Sea Mar leadership has agreed to provide staff time and support to facilitate the program, including analytic, training, and tracking activities. It will also allow research staff to conduct fidelity assessments and chart abstractors to confirm follow-up colonoscopy receipt. Sea Mar has identified a clinic "champion" to serve on the advisory committee and to provide clinical expertise for patient navigation. Ongoing meetings have been held with Sea Mar staff to develop and refine the concept for this proposal. We plan to use an intention-to-treat analysis and are confident that we can identify 1,186 patients each year with an abnormal FIT result, and that an estimated 949 (80%) will be found to have a moderate or low probability of adherence and will be randomized into the trial. We plan an 18-month enrollment period to account for navigator training time and to meet recruitment targets for the study.

Current clinical processes. When a patient is found to have an abnormal FIT result, the provider or team assistant generally informs the patient by phone and places a referral in the EHR. A referral coordinator then phones the patient, provides information about the GI office, and transfers the patient's medical record information to that office. Unreachable patients are mailed a letter. The GI office then phones the patient to schedule an appointment for an office visit (if the patient has not had a previous colonoscopy) or a phone consult (if the patient has). The process is "hit or miss," and many patients do not receive more than one phone call or mailed notification regarding the need for follow-up. While the median wait time to schedule a colonoscopy appointment in STOP CRC was 62 days, backlogs for some GI providers and missed or canceled appointments can lead some patients to experience up to a year-long wait for a colonoscopy (as noted in qualitative interviews with patients [see C.2.]). By addressing the factors that contribute to extended wait-times, patient navigation has been shown to reduce wait times in multiple studies.[42] When patients complete a colonoscopy, their procedure and pathology reports are usually forwarded to clinics (at separate times) and sometimes omit information about when the patients should get screened next.

C.4. Phase I: Validate risk-predication model, assess patient risk, and adapt program materials. We

have developed the risk model using data from safety net clinics (see STOP CRC; C.2.) In partnership with clinicians and patients, we will apply the risk-prediction model to Sea Mar's patient database, risk-stratify patients for adherence to follow-up colonoscopy, and adapt patient navigation protocols and templates using the replication guide from the NHCRCSP and consultation with Dr. Hannon. The adaptation will incorporate local resources (e.g., low-cost colonoscopy services, local transportation services) and knowledge gained from the replication study, led by Dr. Hannon.

Externally validate risk-prediction model in Sea Mar patient database. Our risk score has already been shown to perform adequately in a safety net population (see C.2.). In phase 1, we will apply it to the EHR data at Sea Mar and anticipate achieving good capture of data: in STOP CRC data, only 4.2% of records were missing race, 0.4% were missing Hispanic ethnicity, and 0.3% were missing language. Dr. Mummadi (GI provider and project co-I) guided the development of the model and will guide its validation.

We will externally validate the prediction model in a distinct cohort of Sea Mar patients. This cohort will include patients who had a positive FIT more than a year earlier. In contrast, our study cohort is prospective and will include patients who have a positive FIT result. The eligiblity criteria for both cohorts will be the same as the development cohort of patients in the STOP CRC trial (see C.2.). Specifically, patients will be 50-75 years old and have a positive FIT, which requires follow-up with colonoscopy. Consistent with STOP CRC, patients will have already been excluded if they have EHR evidence of a prior CRC screening (colonoscopy within the past 9 years, fecal testing in the past year), colon disease (e.g., ulcerative colitis or Crohn's disease) or have a shortened life span. We will calculate the predicted probability of obtaining a colonoscopy for individuals in the Sea Mar cohort based on the Cox regression model's exact linear predictor (i.e., coefficients derived from the STOP CRC cohort). While we anticipate high capture of data elements for the risk model, if any of the required predictor characteristics are missing, we will impute their values using multiple imputation with chained equations (MICE).[43-45] We will apply the statistical methods for external validation recommended by the Prognosis Research Strategy (PROGRESS) Group.[46]

We will determine the external validation's separation (discrimation) of low- and moderate- probability patients by calculating the c-statistic and comparing it with the development cohort's c-statistic.[47,48] A drop in the c-statistic of 0.05 or more will be considered inferior separation of patients. We will also calculate the R^2-statistic based on the D-statistic to assess the explained variation.[49] We will divide the Sea Mar cohort into quintiles based on probability of colonoscopy, and assess accuracy (calibration) graphically by plotting the mean predicted risk and the Kaplan-Meier observed risk of colonoscopy.[47,48] We will refine the model by updating the predictions using the Sea Mar baseline rate of colonoscopy to improve agreement between observed and predicted probabilities of colonoscopy,[48] or recalibrating the model's predictor coefficients by fitting a new Cox regression within the Sea Mar cohort.[48] This is consistent with standard procedures for model validation.[8,50]

Assess patients' probability of colonoscopy adherence. Project staff will use the risk-prediction model to group patients according to the probability that they will obtain a follow-up colonoscopy (high, moderate, or low). Mr. Boxberger (IT consultant) will develop an interactive, secure database that Sea Mar and project staff can access. The database will automatically populate de-identified EHR information from patients with a positive FIT result, assign them a unique study identifier, and pull data from eight variables that comprise the risk-prediction model. The CHR biostatistician (Dr. Leo) will run the risk-prediction model and categorize patients according to the probability that they will obtain a colonoscopy, with the bottom two quintiles representing the lowest probability, the middle two quintiles representing moderate probability, and the upper quintile representing the highest probability. After assigning probability, Dr. Leo will remove patients in the highest probability quintile, stratify the remaining patients based on probability category (moderate vs. low), and randomize patients within stratum to receive either the patient navigation intervention or usual care.

Expand advisory board. We will expand the STOP CRC advisory board (consisting of clinic constituents, payers, policy-makers and patients) to include additional clinic constituents and GI providers (see Letters of Support). Dr. Coronado will also serve as a member of the advisory board. The advisory board will meet quarterly throughout the study. Meetings will be organized and facilitated by Dr. Coronado, who facilitates advisory board meetings for STOP CRC.

Adapt patient navigation program materials based on local resources. We will work with Dr. Hannon to review

the NHCRCSP replication manual developed by the Centers for Disease Control.[5] The NHCRCSP translated colonoscopy preparation instructions into 26 languages. The program enrolled adults who qualified for the CDC Breast and Cervical Cancer Program and offered them free colonoscopies. Our program will rely on usual clinical and community resources for colonoscopy. While some materials can be used without modification, we anticipate that some will need to be tailored to the local environment and resources. Leadership at our participating clinics has already noted a desire to minimize duplicate data entry, and for patient navigation phone encounters to be documented in the EHR. For this reason, we will develop materials to train staff in standard documentation procedures. We will obtain local information about referring GI sites, colonoscopy prep used, and resources for low-cost colonoscopy, including ways to enroll in insurance plans and community programs for donated colonoscopies. Where needed, we will solicit feedback on materials from members of our advisory board as well as members of patient advisory councils of participating clinics, as we successfully accomplished in STOP CRC (see C.2.).

Patient navigation protocol. The patient navigation aspect of the program will be built on strong clinic and community partnerships to improve adherence to follow-up colonoscopy and reduce time to resolution and/or recommended treatment. The program consists of six topic-specific contacts that address barriers, bowel preparation, transportation and patient escort plans, post-colonoscopy support, and patients' understanding of results and rescreening interval (further details are provided in Table 4). During each phone call, navigators will assess patients' understanding of each step in undertaking a colonoscopy (e.g., obtaining laxative, finding someone to accompany them to the procedure), gather and document barriers, and obtain/ confirm emergency contact numbers. Patient navigators will use video-phone calls, as available and consistent with patient preference. Across sites, navigators will meet regularly with the project team to discuss barriers and solutions for overcoming barriers (e.g., weekly for the first 3 months, then every 2 weeks). Dr. Hannon will provide ongoing consultation by attending quarterly phone meetings with patient navigators; Dr. Wilborn will attend patient navigator meetings, as needed, to address clinical questions.

Table 4. Patient Navigation Protocol: 6 Topic-Specific Calls

N	Objective	Timing (relative to colonoscopy)
1	Obtain agreement for colonoscopy, confirm appointment scheduling, establish rapport, -assess barriers	NA
2	Review bowel prep instructions, how to obtain bowel prep, address barriers, confirm transportation plans	5 - 7 days before
3	Review bowel prep instructions, address remaining challenges	1 -2 days before
4	Confirm appointment details, discuss bowel prep progress, answer remaining questions	1 day before
5	Evaluate colonoscopy experience, provide post-procedure support	Day of/after
6	Confirm patient receipt/ understanding of results/ recommended rescreening interval	2 - 4 weeks after

Patient navigators will help patients receive needed care. In Washington state (where all participating clinics are located), King County Public Health and the Washington State Department of Health have considerable experience providing free CRC screening and follow-up care to uninsured individuals as part of the Washington state Breast, Cervical, and Colon Health Program (BCCHP).[51] Medical care after diagnosis is a covered Medicaid benefit and tracked through state cancer registries. The BCCHP also pays for diagnostic colonoscopy among patients who have abnormal FIT results and meet income eligibility thresholds (≤250% of the poverty level).

In the proposed study, an estimated 462 adults will screen positive on a FIT and be randomized to receive patient navigation. Based on estimates from the NHCRCSP, navigation will require 126 total minutes per patient (or 970 hours [462 X 126 minutes] on average).[52] Our budget includes a clinic impact fee to cover this cost. In the NHCRCSP, navigators interacted with an average of 5-8 patients per day.

Patient navigator training. Sea Mar leaders have identified a clinic champion for the program (Dr. Timmons) and plan to hire a new patient navigator for this project. All navigators will have access to medical records to identify patients with abnormal FIT results. Consistent with the NHCRCSP and the experience of Dr. Hannon, patient navigators will either be nurse practitioners or have a similar clinical role. Training in the NHCRCSP will be co-delivered by Ms. Rivelli, a bilingual (English and Spanish) mental health counselor and qualitative researcher, and Dr. Hannon. Ms. Rivelli has led Spanish-language motivational interviewer trainings for STOP CRC (see C.2.). Consistent with the original program, training will consist of a two-day didactic session followed by eight weeks of coaching and feedback to ensure that patient navigators successfully complete the

six-topic phone protocol and tracking procedures.

The final part of the training will address tracking; navigators will record telephone encounters in the EHR. In addition, they will maintain logs that record: (1) referrals to community resources, (2) patient barriers, and (3) patients' canceled and rescheduled appointments. Dr. Hannon will work with Ms. Rivelli to administer a training competency checklist and a fidelity assessment (see C.5.) to ensure that all patient navigators achieve an established competency and that the program is delivered as intended.

C.5. Phase II: Assess the effectiveness and cost-effectiveness of patient navigation. We will conduct a large-scale, targeted, patient-randomized controlled trial that will include ~1200 patients at 28 Sea Mar clinics. We will compare rates of follow-up colonoscopy completion in ~900 patients having either a moderate or low risk of colonoscopy adherence who are randomized to receive either a telephone-based program of patient navigation delivered by trained clinical staff or usual care. We will assess the cost and cost-effectiveness of the program overall and for patient groups defined by risk level (moderate or low risk of adhering to follow-up colonoscopy). Wewill also assess differences in secondary outcomes (e.g., time to colonoscopy receipt, appointment cancelations and no-shows, colonoscopy quality), report process outcomes (e.g., intervention delivery), and explore possible moderators of effectiveness (e.g. intervention dose; patient demographic characteristics, including sex). Qualitative interviews conducted among patients, patient navigators, and clinical staff will elucidate reactions to the program, unintended consequences, and remaining barriers to follow-up.

Randomization. Dr. Leo will run the risk-prediction model (see C.4.) and categorize patients according to their probability of receiving a follow-up colonoscopy (high, moderate, and low). Patients in the highest probability category will receive surveillance (Table 5). Dr. Leo will then randomize patients with either moderate or low probability of adherence using a stratified approach that considers probability level, age group (50-64 vs. 65-74), and sex. **In this way, we will consider sex a key biological variable.** The research staff (with the exception of Dr. Leo) and clinical staff will be blinded to probability of adherence. For practical reasons, neither the research team nor the clinic staff will be blinded to randomization assignment. The randomization will result in 462 patients assigned to the patient navigation arm and 462 assigned to the usual care arm. We will assess rates of colonoscopy receipt in the group categorized as having high probability of adherence (i.e., surveillance group). At the end of the evaluation, if the intervention is found to be successful, it will be offered to all patients in the usual care and surveillance arms who did not get a follow-up colonoscopy.

Table 5. Proposed Patient Randomization Assignment*

	Probability of follow-up colonoscopy		
	Low	**Moderate**	**High**
Patient navigation	231	231	
Usual care	231	231	
Surveillance			231

*total number 1040, excludes 3.5% of patients who are estimated to have a prior recent colonoscopy

Fidelity assessment and intervention dose (scientific rigor). Our fidelity assessment will be designed in accordance with established methods outlined by the NIH Behavior Change Treatment Fidelity Workgroup[53,54] and will focus on: (1) the accuracy of data capture for our primary and secondary outcomes (measurement fidelity), and (2) rigor and consistency with which the intervention is delivered (intervention fidelity). As part of intervention fidelity, we will assess the intervention dose.

To address measurement fidelity and ensure full capture of colonoscopy receipt 1 year following the intervention, our chart auditor (Ms. Olsen) will review charts from patients who had a positive FIT result and have no EHR evidence of a follow-up colonoscopy (found using EHR procedure codes). Based on our chart abstraction for STOP CRC, about 80% of colonoscopy reports in the records of primary care were retrievable with electronic codes (e.g., procedure codes).[55] During chart audits, Ms. Olsen will be blinded to randomization assignment. When a follow-up colonoscopy is not found during the audit, she will record the reason (e.g., excluded for medical reasons, had a recent prior colonoscopy, patient refusal). Where a colonoscopy is found, Ms. Olsen will record date of the procedure, whether a pathology report is available, and if so, the findings on pathology (e.g., advanced adenoma, cancer). In STOP CRC (C.2.), chart audits took about 15 minutes per chart to complete. In addition, project leads at Sea Mar will request information from patients who were referred to a given GI facility. The information request will ask GI staff to provide: (1) procedure or pathology

reports where they are missing in primary care; (2) dates of any canceled GI appointments/ no shows; (3) documented reasons that the patient did not receive a colonoscopy; (4) measures of colonoscopy quality (e.g., adequacy of prep and completeness of colonoscopy); and (5) date and how results were delivered to patient.

To address intervention fidelity, we will record 25% of all telephone contacts during the first 3 months of the program (and during a new navigator's first 3 months). Patients will be asked to provide verbal consent for the recording (this was successful in a previous study led by Dr. Coronado[56]). Project staff will review these recordings for content and timing, and identify areas for improvement, as well as assess EHR charts for accurate capture of phone call information. For phone calls delivered beyond 3 months, 5% will be recorded and their corresponding charts will be reviewed for content, timing, and accurate capture. Any issues will be addressed during ongoing meetings and booster training sessions. Qualitative patient interviews at the end of the program (n = 60) will gather patient-reported information on receipt of each call type, consistent with the NHCRCSP.[52] We will track and document any changes to usual care by reviewing a subset (10% sample) of telephone encounters for patients assigned to usual care. **Thus, we will assess possible contamination.**

Intervention dose. As part of the fidelity assessment, we will track consistency of intervention dose: the number and content of phone calls delivered by patient navigators based on EHR telephone encounters. The standard protocol includes six timed phone calls that address pre-defined content areas; thus, dose will be calculated as the proportion of phone calls completed and/or content areas addressed (with 6 as the denominator).

Primary outcome: Assessment of effectiveness. Our primary outcome is whether patients obtain a follow-up colonoscopy within 1 year of having a positive FIT result, as assessed through chart audit. All analyses will rely on intention-to-treat; that is, patients will retain their randomization assignment irrespective of whether or not they received patient navigation. We will conduct statistical analyses using Stata 13.2 and hierarchical linear modeling software.[57] Our primary and secondary outcomes and process measures are displayed in Table 6.

Sea Mar's EHR data will be transferred to CHR each quarter via a secure file transfer. We will examine the distribution of all variables prior to analyses and verify all missing and out-of-range values. We will use hierarchical generalized linear modeling[57-59] to account for clustering of patients within clinics. Because the primary outcome is binary (i.e., follow-up colonoscopy, yes/no), we will use a model with a logit link and binomial distribution (i.e., multilevel logistic regression). The independent variable will be arm (dummy-coded) with usual care as the reference group. 'Clinic' will be modeled as a random effect. Odds ratios >1 support the hypothesis that patient navigation has a higher follow-up rate than usual care.

Table 6. Schedule of Measures for Phase 2

Variable	Data source	How measured	CCM domain	Time point B	Time point FU
Phase 2/ Aim 2: Primary Outcome					
Receipt of colonoscopy within 1 year of abnormal FIT result	EHR[1]	N who complete a colonoscopy/ N screen FIT+ (Yes/No)	DR	√	√
Cost and cost-effectiveness	EHR. Navigator logs	Time spent delivering intervention components/ training*salary; cost per person who obtains follow-up, number needed to treat	DR	√	√
Phase 2/ Aim 3: Secondary Outcomes					
Time to colonoscopy receipt	EHR[1]	Time to colonoscopy (days)[2]	DR	√	√
Time to initiation of cancer treatment	EHR[1]	Time to cancer tx (days)	DR	√	√
Missed appointments / no shows	GI records	N missed, no show appts / N colonoscopies scheduled	DR	√	√
GI appointment cancelations	GI records	N cancelations w/I 24 hrs of appt / N colonoscopies scheduled			
Colonoscopy quality (adequate colonoscopy preparation; completeness of exam (cecum reached).	EHR[1]	N adequate bowel prep / N with a performed colonoscopy; % with cecum reached.	DR	√	√
Colonoscopy outcomes (% adenomas detected; n cancers found; stage of detection)	EHR[1] (pathology report)	N adenomas detected / N colonoscopies performed, N cancers found/ N colonoscopies performed, cancer stage	DR	√	√
Phase 2/ Aim 3: Moderators of treatment effect					
Risk strata (moderate, low probability), patient characteristics (age, sex, insurance status, preferred language, CRC screening hx, co-morbidities)	EHR[1]	Frequencies of relevant characteristics	NA	√	√
Phase 2: Intervention Fidelity Assessment/ Dose					
Patient navigator training checklist	NHCRCSP guide	N completed all competencies	SS	On-going	
N phone calls completed per patient	EHR[1]	N phone calls/ N anticipated	SS	On-going	
N content areas addressed (of 6)	EHR[1]/ navigator logs	N content areas / 6	SS	On-going	
Phase 2: Reaction to program					
Patient barriers; reaction/satisfaction with program; unintended consequences, and persistent barriers to follow-up	Interview data	Debrief interviews with practice facilitators, patient navigators, and one-on-one interviews with patients	DR		√

[1]EHR – electronic health record; charts will be requested from GI as needed. [2]among eligible patients with an abnormal FIT result; HCL = Health Center Leader; PCP = Primary care provider; GI = Gastroenterology; DS = evidence-based decision support, IS = clinical information systems, DR = delivery system redesign, HO = health care organization, SS = self-management support, and CR = community resources

Sample size and power. Based on data from our STOP CRC clinics (see C.2.), we expect that 44% of patients in the usual care arm with moderate or low probability of adherence will complete a follow-up colonoscopy within 1 year. Based on our STOP CRC results, we expect that 1,186 adults will have a positive FIT result each year. Assuming that 3.5% of patients with positive FITs will not need a colonoscopy because of a recently completed colonoscopy, resolved endoscopy, or contra-indication,[39,60] and enrolling the top 80% with a moderate or low probability of obtaining a colonoscopy, we estimated power using a sample size of 924 abnormal FIT results. Even in patient-randomized trials, it is important to account for the intraclass correlation (ICC) from patients nested within clinics.[61-64] Estimates of the ICC at the clinic level for CRC screening collected from several different studies range from .001 to .10, with the majority ranging from .02 to .05.[65] The ICC for STOP CRC is .03 (see C.2.). Though we anticipate a lower ICC for this study given that we will partner with a single large FQHC with more uniform procedures and practices (i.e., less between-clinic variability) rather than eight smaller FQHCs in the STOP CRC trial, we will use an ICC estimate of .03 as a conservative upper estimate. Given that larger ICCs increase the design effect and reduce the power of the test, wewill provide the minimum detectable odds ratios for the primary outcome for both a near zero ICC and an ICC of .03; we will base our analyses on an average cluster size of 33 patients per clinic (924 abnormal FIT patients/28 clinics).[66] In a logistic regression framework, we will have 80% power to detect a difference of 12.9% (completion rate in intervention of 56.9%, OR=1.68) when accounting for the design effect and a difference of 9.2% (completion rate in intervention of 53.2%, OR=1.45), assuming no design effect at a two-tailed alpha level of .05.[67,68] We believe a difference between 9.2% and 12.9% is both achievable and clinically significant. Notably, our minimal detectable difference is 2-3 times lower that the effect size reported in the NHCRCSP (27 percentage points).[5]

Assessment of cost and cost-effectiveness. Once we have established the effectiveness of the patient navigation program, we will assess costs and cost-effectiveness from the health-plan perspective, both overall

and by risk stratum (moderate- vs. low-probability of adherence). This information will be invaluable for systems hoping to implement such programs. We will follow best practices and be guided by previous economic analyses of patient navigation for CRC screening follow-up.[69] First, we will assess the costs of implementing and maintaining the patient navigation program and estimate how costs of patient navigation differ when delivering the service to all patients, versus just those who have a moderate or low probability of undergoing a colonoscopy. Next, using the framework of cost-effectiveness, we will estimate the incremental cost-effectiveness ratio (ICER) as: (1) cost per additional completed colonoscopy, (2) cost per additional adenoma detected, and 3) cost per additional cancer detected. Finally, to further evaluate the impact of specific program elements on overall cost, we will conduct a budget-impact analysis.

Consistent with our previous economic evaluation of CRC screening interventions,[70] costs collected will include those of (1) medical care related to cancer detection (e.g., colonoscopy, re-screening) and (2) the intervention delivery. Costs of cancer care will not be included. We will identify follow-up colonoscopy events and re-screening using EHR data, and apply costs using standard Medicare fee schedules. Intervention delivery costs will include health plan project management, patient identification, patient tracking, and navigator time, among others. Resources used to deliver the intervention will be identified using staff logs, interviews, and budget information. We will use national sources for wage rates for clinic and other staff (e.g., programmer) time.[71] Research and non-research costs will be separated after discussion with intervention and project staff, and we will undertake a sensitivity analysis focused on replication costs (those costs most likely to be part of implementation).[72] We will focus on near-term (within 1 year of positive FIT) costs and effects of the program, as our experience suggests those analyses are of most interest to decision-makers; costs will not be discounted owing to the 1-year timeframe.

We will estimate the intervention's ICERs using net benefit regression methods[73,74] and will construct cost-effectiveness acceptability curves to illustrate the probability of navigation being cost-effective across a range of willingness-to-pay values.[75,76] Using net benefit regression, we will evaluate differences in cost-effectiveness by subgroups, including baseline probability of adherence (moderate vs. low). After inspection, costs between the arms will be compared using methods appropriate for cost data (e.g., right-skewness, censored follow-up time) including two part models,[77] bootstrapping[78,79] and inverse probability weighted regression.[80]

While cost-effectiveness is critical to understanding the value of screening improvements, the costs of the navigation will vary depending on the amounts of specific services delivered. To address this, we will conduct budget impact analyses following guidance on best practices.[81] We will develop scenarios to illustrate how intervention costs change when fixed costs are spread over differing population sizes, and how patient population factors influence variable costs. Other scenarios will examine whether costs of navigation can be offset by gains to health systems, such as fewer repeat colonoscopies because of adequate colonoscopy prep and fewer late cancellations and missed appointments/no-shows.[5] We will also assess the number needed to treat (e.g., patient navigation) in each probability stratum to achieve a successful follow-up colonoscopy.

Secondary outcomes and process measures. We will gather data from the EHR on time to colonoscopy completion, time to initiation of cancer treatment, and appointment no-shows and cancelations. Using the pathology report, we will also track colonoscopy-related quality measures, including adequacy of colonoscopy prep, detection of adenomas and cancer, and cancer stage at detection. The anticipated baseline prevalence of our secondary outcomes is given in Table 7.

Table 7. Prevalence of PRECISE Secondary Outcomes

Baseline rates of secondary outcomes	%
Time to colonoscopy receipt (median dys)[a]	62
Missed/ canceled appointments [b]	15.6%
Adequate bowel prep [b]	66[c] - 87.5%[b]
% advanced adenomas	31.0%
% cancer	5.0%

[a]based on STOP CRC; [b]based on NHCRCSP, [c]based on Naylor et al. 2017[1]

We will use the Cox proportional hazards regression model with shared frailty for time to colonoscopy completion and time to initiation of cancer treatment. The shared frailty model is the survival data analog to random effects regression models that can account for the clustering effect of patients within clinics.[82,83] The independent variable will be study arm, which will be coded the same as in the primary outcome analysis. Significant hazard ratios >1 indicate that patient navigation has shorter times to colonoscopy completion and/or initiation of cancer treatment than usual care. We anticipate finding 59 new cancers (1186 abnormal test results * 5% PPV for cancer) and will explore differences by arm in time to initiation of cancer treatment

(recognizing that we may be under-powered to show a significant effect). For binary secondary outcome and process measures (e.g. missed/ canceled appointments, adequacy of bowel prep, intervention dose), we will use the same modeling framework (e.g., multilevel logistic regression) as described for our primary outcome.

Analysis of possible moderators. Notably, our preliminary data showed follow-up colonoscopy receipt varied substantially by probability strata (30%, 59%, and 93% for the low, moderate, and high strata, respectively), suggesting that assessments of clinically meaningful impacts could differ by probability strata. To determine whether adherence probability moderates the effect of the intervention, we will add probability strata (moderate vs. low) and the product of stratum and arm to the primary outcome model. The product represents the interaction of arm and probability stratum; a significant term provides evidence for effect modification. We will determine the nature of any interaction by examining the simple main effects using graphical methods. We will repeat this analysis using the continuous risk score in place of the risk strata. We will have 80% power to detect an odds ratio for the product term, which represents the multiplicative change from the odds ratio for the moderate probability stratum for arm compared to the low probability stratum for arm of 2.98 (or 0.34 in the opposite direction), accounting for the design effect, and 2.17 (or 0.46 in the opposite direction) assuming no design effect, at a two-tailed alpha level of .05.[67]

Previous literature has reported significant differences in the effectiveness of patient navigation for colorectal cancer *screening* across patient subgroups defined by sex (patient navigation was more effective in women vs. men),[84] preferred language (patient navigation was more effective in patients who preferred Spanish vs. English)[85] and co-morbidities (patient navigation was more effective in patients with co-morbidity score >2 vs <= 2)[42], and age (patient navigation was more effective in 65-69 vs. 70-75 age groups).[86] We will use the same methods as above to determine whether these and other patient characteristics (e.g., insurance status, income, previous CRC screening history) moderate the effect of the intervention. We will perform separate analysis for each patient moderator. Because the examination of the moderating effects of patient characteristics is secondary and exploratory, this study is not formally powered for these analyses. Given the inherent lower power of moderator analyses, we will focus on themagnitude of product term coefficients.[87,88]

Qualitative interviews with patients and patient navigators. To further explore issues regarding program implementation, we will conduct qualitative interviews with patients and patient navigators as well as clinic staff and GI office staff and providers. Qualitative interviews offer deeper, more specific detail on the process, which will be invaluable in refining patient navigation When coupled with the results of our cost evaluations, this study will provide both systems and care-level data on how to best implement such a program. Our qualitative team, Ms. Schneider and Ms. Rivelli, will conduct one-on-one phone interviews (n=~60) with a sample of patients at various Sea Mar clinics from both risk categories (moderate and low) who were due for follow-up colonoscopy and were screened, as well as a sample of patients who were not screened. Utilizing the EHR tracking data, we will use purposive sampling to select patients across patient characteristics.[89] The interviews will assess persistent barriers that hinder participation in colonoscopy and identify program components that could enhance effectiveness. Spanish-language interviews will be conducted by Ms. Rivelli (bilingual in English and Spanish). Interviews will explore reasons for getting or not getting a follow-up colonoscopy, as well as awareness of colonoscopy, previous CRC screening history, and understanding of colonoscopy prep, social support, and general reaction to and receipt of the program. We will also gather any unanticipated consequences of the program (both positive and negative). Patients will be offered $25 as a token of appreciation for their time.

Ms. Schneider will conduct one-on-one debrief interviews with patient navigators and identified clinic leadership/ staff and GI office staff/providers to understand adaptations to the program and factors that could influence sustainability. Clinic staff will be selected as those who are involved in CRC follow-up processes at Sea Mar, and GI office staff and providers will be selected from representative practices. We anticipate conducting 25-30 interviews (among 20 unique individuals) with patient navigators, clinic and GI staff over the course of the intervention. These interviews also will explore unanticipated consequences and persistent barriers to follow-up colonoscopy. Findings from the interviews will inform implementation of the patient navigation program and content for dissemination materials.

All qualitative interviews will be transcribed, coded in Atlas.ti (a qualitative software program), and analyzed using a content analysis approach.[90-92] Analysis will also be guided by constructs within our conceptual model

(CCM) as well as identification of emergent themes arising from use of grounded theory technique.[93] Disagreement will be resolved through consensus. Additionally, we will consult our advisory board, whose members will review de-identified data and assist in interpreting the findings.

C.6. Sustainability, dissemination and study strengths and limitations.

Sustainability plan. We have several strategies for long-term sustainability. First, we will embed the prediction-risk model into the EHR so that patients' risks are calculated in real time. Sea Mar is interested in sustaining effective programs to address follow-up colonoscopy receipt over the long term. In addition, we have obtained initial commitments from payers and coordinated care organizations that currently fund efforts to support clinics in quality improvement (see Letters of Support).

Dissemination plan. Given that a replication manual for the NHCRCSP has been produced by CDC, our dissemination plan will focus on sharing the specifications of our risk-prediction model and developing the clinical decision support tools to enable its sustainable use. We will develop a prediction-model specifications guide. We will present our overall study findings at a board of directors meeting at Sea Mar, provider meetings and retreats, and local conferences. We post our guide on NCI research-tested intervention programs and other national implementation websites. We will support the use of testimonials and other motivational messages in e-health coaching devices, such as those developed by Ginger.io,[94] that deliver patient advice and coaching through smartphone applications and text messages.

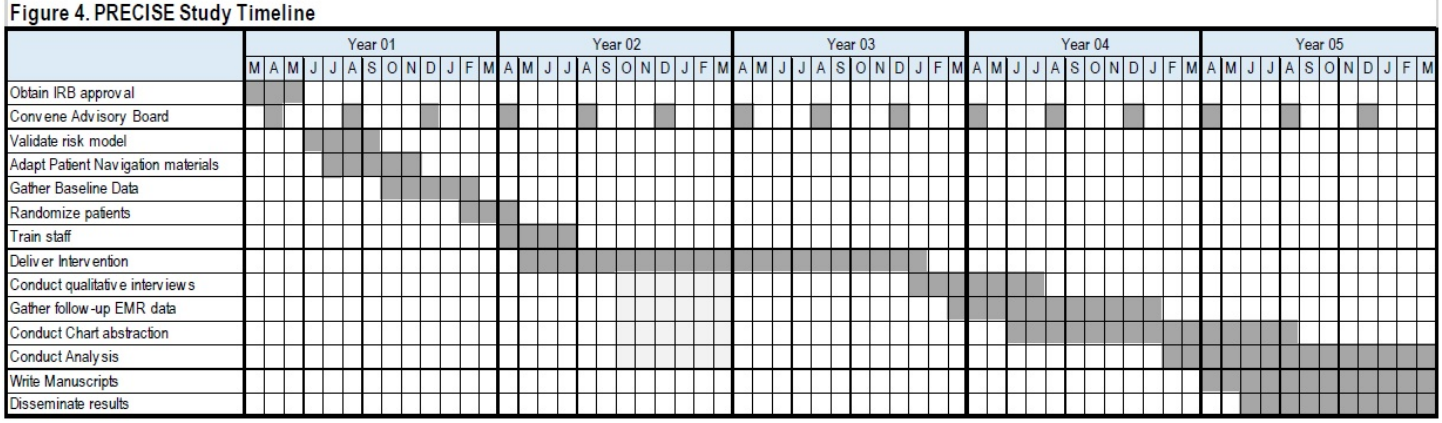
Study limitations, strengths, and timeline

Limitations. (1) We are conducting this research in safety net clinics, so will likely encounter barriers inherent to research in real-world delivery systems. Based on our experience in this setting, we will adjust to changing clinical processes and patient needs as the study progresses. (2) Although we will have sufficient power to assess whether the intervention effect is moderated by probability of adherence, we may be underpowered to assess some potential moderators. Nonetheless, our study will be 4 times larger than any previous evaluation of follow-up colonoscopy navigation. (3) The enthusiastic involvement of clinic leadership has been essential to our planning process and may not be replicable in all CHCs.

Strengths. (1) The study setting provides an opportunity to conduct a randomized trial within a large, diverse health center that primarily uses FIT for first-line CRC screening and will yield high data capture. (2) Our study clinics serve socio-demographically diverse patients; we will analyze differences in intervention effect across patient characteristics, including sex. (3) Our team members have collaborated on similar research with multiple successes in CRC screening and pragmatic implementation research. The PI has ongoing collaborations with the partnering health center. (4) Our design will answer a unique pragmatic question: is patient navigation an effective approach to address low rates of follow-up colonoscopy among those unlikely to adhere? Secondarily, does the effectiveness of patient navigation differ by patients' probability of non-adherence? (5) If successful, our program could allow health systems to focus their patient navigation targets, overcome key barriers to sustaining patient navigation programs, and catalyze sustained impact on the field.

Timeline. A timeline is provided in Figure 4; it shows timing of Phase I (validating the risk prediction model, adapting navigation materials) and Phase II activities (patient navigation, and analysis and report-writing).

Figure 4. PRECISE Study Timeline



Bibliography And References Cited

1. Naylor K, Fritz C, Polite B, Kim K. Evaluating screening colonoscopy quality in an uninsured urban population following patient navigation. *Prev Med Rep.* 2017;5:194-199.
2. Freund KM, Battaglia TA, Calhoun E, Darnell JS, Dudley DJ, Fiscella K, Hare ML, LaVerda N, Lee JH, Levine P, Murray DM, Patierno SR, Raich PC, Roetzheim RG, Simon M, Snyder FR, Warren-Mears V, Whitley EM, Winters P, Young GS, Paskett ED, Writing Group of the Patient Navigation Research P. Impact of patient navigation on timely cancer care: the Patient Navigation Research Program. *J Natl Cancer Inst.* 2014;106(6):dju115.
3. Raich PC, Whitley EM, Thorland W, Valverde P, Fairclough D, Denver Patient Navigation Research P. Patient navigation improves cancer diagnostic resolution: an individually randomized clinical trial in an underserved population. *Cancer Epidemiol Biomarkers Prev.* 2012;21(10):1629-1638.
4. Paskett ED, Katz ML, Post DM, Pennell ML, Young GS, Seiber EE, Harrop JP, DeGraffinreid CR, Tatum CM, Dean JA, Murray DM, Ohio Patient Navigation Research P. The Ohio Patient Navigation Research Program: does the American Cancer Society patient navigation model improve time to resolution in patients with abnormal screening tests? *Cancer Epidemiol Biomarkers Prev.* 2012;21(10):1620-1628.
5. Rice K, Gressard L, DeGroff A, Gersten J, Robie J, Leadbetter S, Glover-Kudon R, Butterly L. Increasing colonoscopy screening in disparate populations: Results from an evaluation of patient navigation in the New Hampshire Colorectal Cancer Screening Program. *Cancer.* 2017 May 2. [Epub 2017 May 2]
6. Raich PC, Whitley EM, Thorland W, Valverde P, Fairclough D. Patient navigation improves cancer diagnostic resolution: an individually randomized clinical trial in an underserved population. *Cancer Epidemiol Biomarkers Prev.* 2012;21(10):1629-1638.
7. Hayward RA, Kent DM, Vijan S, Hofer TP. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. *BMC Med Res Methodol.* 2006;6:18.
8. Kent DM, Nelson J, Dahabreh IJ, Rothwell PM, Altman DG, Hayward RA. Risk and treatment effect heterogeneity: re-analysis of individual participant data from 32 large clinical trials. *Int J Epidemiol.* 2016 Dec 1;45(6):2075-2088.
9. Guy GP Jr, Richardson LC, Pignone MP, Plescia M. Costs and benefits of an organized fecal immunochemical test-based colorectal cancer screening program in the United States. *Cancer.* 2014;120(15):2308-2315.
10. Meester RG, Zauber AG, Doubeni CA, Jensen CD, Quinn VP, Helfand M, Dominitz JA, Levin TR, Corley DA, Lansdorp-Vogelaar I. Consequences of Increasing Time to Colonoscopy Examination After Positive Result From Fecal Colorectal Cancer Screening Test. *Clin Gastroenterol Hepatol.* 2016;14(10):1445-1451.e1448.
11. Carlson CM, Kirby KA, Casadei MA, Partin MR, Kistler CE, Walter LC. Lack of follow-up after fecal occult blood testing in older adults: inappropriate screening or failure to follow up? *Arch Intern Med.* 2011;171(3):249-256.
12. Van Kleek E, Liu S, Conn LM, Hoadley A, Ho SB. Improving the effectiveness of fecal occult blood testing in a primary care clinic by direct colonoscopy referral for positive tests. *J Healthc Qual.* 2010;32(6):62-69.
13. Partin MR, Burgess DJ, Burgess JF, Jr., Gravely A, Haggstrom DA, Lillie SE, Nugent S, Powell AA, Shaukat A, Walter LC, Nelson DB. Organizational predictors of colonoscopy follow-up for positive fecal occult blood test results: an observational study. *Cancer Epidemiol Biomarkers Prev.* 2015 Feb;24(2):422-34.
14. Kistler CE, Kirby KA, Lee D, Casadei MA, Walter LC. Long-term outcomes following positive fecal occult blood test results in older adults: benefits and burdens. *Arch Intern Med.* 2011;171(15):1344- 1351.
15. Green BB, Anderson ML, Wang CY, Vernon SW, Chubak J, Meenan RT, Fuller S. Results of Nurse Navigator Follow-up After Positive Colorectal Cancer Screening Test: A Randomized Trial. *J Am Board Fam Med.* 2014;27(6):789-795.
16. Miglioretti DL, Rutter CM, Bradford SC, Zauber AG, Kessler LG, Feuer EJ, Grossman DC. Improvement in the diagnostic evaluation of a positive fecal occult blood test in an integrated health care organization. *Med Care.* 2008;46(9 Suppl 1):S91-96.
17. Liss DT, Brown T, Lee JY, Altergott M, Buchanan DR, Newland A, Park JN, Rittner SS, Baker DW. Diagnostic colonoscopy following a positive fecal occult blood test in community health center patients. *Cancer Causes Control.* 2016;27(7):881-887.
18. Oluloro A, Petrik AF, Turner A, Kapka T, Rivelli J, Carney PA, Saha S, Coronado GD. Timeliness of

Colonoscopy After Abnormal Fecal Test Results in a Safety Net Practice. *J Community Health.* 2016;41(4):864-870.
19. National Association of Community Health Centers. America's Health Centers.08/2011. www.nachc.com/research. Accessed 03/26/2012.
20. National Association of Community Health Centers. Expanding Health Centers under Health Care Reform:Doubling Patient Capacity and Bringing Down Costs. 06/2010. www.nachc.com/research. Accessed 03/26/2012.
21. Krok-Schoen JL, Kurta ML, Weier RC, Young GS, Carey AB, Tatum CM, Paskett ED. Clinic type and patient characteristics affecting time to resolution after an abnormal cancer-screening exam. *Cancer Epidemiol Biomarkers Prev.* 2015;24(1):162-168.
22. National Colorectal Cancer Roundtable. Tools & Resources – 80% by 2018. 2016. http://nccrt.org/tools/80-percent-by-2018/. Accessed 12/28/2016.
23. Butterly L. Implementing a Quality Screening Navigation Program. Paper presented at: 80% by 2018 Forum: Increasing CRC Screening Rates 2015; Bethesda, MD.
24. Elkin EB, Shapiro E, Snow JG, Zauber AG, Krauskopf MS. The economic impact of a patient navigator program to increase screening colonoscopy. *Cancer.* 2012;118(23):5982-5988.
25. Meenan RT, Anderson ML, Chubak J, Vernon SW, Fuller S, Wang CY, Green BB. An economic evaluation of colorectal cancer screening in primary care practice. *Am J Prev Med.*2015;48(6):714-721.
26. Lairson DR, Dicarlo M, Deshmuk AA, Fagan HB, Sifri R, Katurakes N, Cocroft J, Sendecki J, Swan H, Vernon SW, Myers RE. Cost-effectiveness of a standard intervention versus a navigated intervention on colorectal cancer screening use in primary care. *Cancer.* 2014;120(7):1042-1049.
27. Jandorf L, Stossel LM, Cooperman JL, Graff Zivin J, Ladabaum U, Hall D, Thelemaque LD, Redd W, Itzkowitz SH. Cost analysis of a patient navigation system to increase screening colonoscopy adherence among urban minorities. *Cancer.* 2013;119(3):612-620.
28. Stiell IG, Clement CM, Grimshaw J, Brison RJ, Rowe BH, Schull MJ, Lee JS, Brehaut J, McKnight RD, Eisenhauer MA, Dreyer J, Letovsky E, Rutledge T, MacPhail I, Ross S, Shah A, Perry JJ, Holroyd BR, Ip U, Lesiuk H, Wells GA. Implementation of the Canadian C-Spine Rule: prospective 12 centre cluster randomised trial. *BMJ.* 2009;339:b4146.
29. Parikh RB, Kakad M, Bates DW. Integrating Predictive Analytics Into High-Value Care: The Dawn of Precision Delivery. *JAMA.* 2016;315(7):651-652.
30. Insititute for Healthcare Improvement. Quality, Cost, and Value. 2016. http://www.ihi.org/Topics/QualityCostValue/Pages/default.aspx. Accessed October 1,2016.
31. Percac-Lima S, Ashburner JM, Zai AH, Chang Y, Oo SA, Guimaraes E, Atlas SJ. Patient Navigation for Comprehensive Cancer Screening in High-Risk Patients Using a Population-Based Health Information Technology System: A Randomized Clinical Trial. *JAMA Intern Med.* 2016;176(7):930-937.
32. Blumenthal DM, Singal G, Mangla SS, Macklin EA, Chung DC. Predicting Non-Adherence with Outpatient Colonoscopy Using a Novel Electronic Tool that Measures Prior Non-Adherence. *J Gen Intern Med.* 2015;30(6):724-731.
33. Wagner EH, Austin BT, Von Korff M. Improving outcomes in chronic illness. *Manag Care Q.* 1996;4(2):12-25.
34. Tsai AC, Morton SC, Mangione CM, Keeler EB. A meta-analysis of interventions to improve carefor chronic illnesses. *Am J Manag Care.* 2005;11(8):478-488.
35. The RAND Evaluation. *Improving Chronic Illness Care* 2006-2010. http://www.improvingchroniccare.org/index.php?p=The_RAND_Evaluation&s=32. Accessed January 1, 2010.
36. Otero-Sabogal R, Owens D, Canchola J, Tabnak F. Improving rescreening in community clinics: does a system approach work? *J Community Health.* 2006;31(6):497-519.
37. Hung DY, Rundall TG, Tallia AF, Cohen DJ, Halpin HA, Crabtree BF. Rethinking prevention in primary care: applying the chronic care model to address health risk behaviors. *Milbank Q.*2007;85(1):69-91.
38. Glasgow RE, Orleans CT, Wagner EH. Does the chronic care model serve also as a template for improving prevention? *Milbank Q.* 2001;79(4):579-612, iv-v.
39. Miglioretti DL, Rutter CM, Bradford SC, Zauber AG, Kessler LG, Feuer EJ, Grossman DC. Improvement in the diagnostic evaluation of a positive fecal occult blood test in an integrated health care organization. *Med Care.* 2008;46(9 Suppl 1):S91-96.
40. Gellad ZF, Almirall D, Provenzale D, Fisher DA. Time from positive screening fecal occult blood test to

colonoscopy and risk of neoplasia. *Dig Dis Sci.* 2009;54(11):2497-2502.
41. Coronado GD, Vollmer WM, Petrik A, Aguirre J, Kapka T, DeVoe J, Puro J, Miers T, Lembach J, Turner A, Sanchez J, Retecki S, Nelson C, Green B. Strategies and opportunities to STOP colon cancer in priority populations: pragmatic pilot study design and outcomes. *BMC Cancer.* 2014;14:55.
42. Whitley EM, Raich PC, Dudley DJ, Freund KM, Paskett ED, Patierno SR, Simon M, Warren-Mears V, Snyder FR. Relation of comorbidities and patient navigation with the time to diagnostic resolution after abnormal cancer screening. *Cancer.* 2017;123(2):312-318.
43. Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing predictor values was preferred. *J Clin Epidemiol.* 2006;59(10):1092-1101.
44. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011;30(4):377-399.
45. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, WoodAM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009;338:b2393.
46. Steyerberg EW, Moons KG, van der Windt DA, Hayden JA, Perel P, Schroter S, Riley RD, Hemingway H, Altman DG. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med.* 2013;10(2):e1001381.
47. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J.* 2014;35(29):1925-1931.
48. Royston P, Altman DG. External validation of a Cox prognostic model: principles and methods. *BMC Med Res Methodol.* 2013;13:33.
49. Royston P. Explained variation for survival models. . *Stata J.* 2006;6:83-96.
50. Burke JF, Hayward RA, Nelson JP, Kent DM. Using internally developed risk models to assess heterogeneity in treatment effects in clinical trials. *Circulation. Cardiovascular quality and outcomes.* 2014;7(1):163-169.
51. Phillips-Angeles E, Song L, Hannon PA, Celedonia M, Stearns S, Edwards K, Feest S, Shumann A. Fostering partnerships and program success. *Cancer.* 2013;119 Suppl 15:2884-2893.
52. DeGroff A, Coa K, Morrissey KG, Rohan E, Slotman B. Key considerations in designing apatient navigation program for colorectal cancer screening. *Health Promot Pract.* 2014;15(4):483-495.
53. Robb SL, Burns DS, Docherty SL, Haase JE. Ensuring treatment fidelity in a multi-site behavioral intervention study: implementing NIH Behavior Change Consortium recommendations in the SMART trial. *Psychooncology.* 2011;20(11):1193-1201.
54. Bellg AJ, Borrelli B, Resnick B, Hecht J, Minicucci DS, Ory M, Ogedegbe G, Orwig D, Ernst D, Czajkowski S. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium. *Health Psychol.* 2004;23(5):443-451.
55. Petrik AF, Green BB, Vollmer WM, Le T, Bachman B, Keast E, Rivelli J, Coronado GD. The validation of electronic health records in accurately identifying patients eligible for colorectal cancer screening in safety net clinics. *Fam Pract.* 2016;33(6):639-643.
56. Coronado GD, Beresford SA, McLerran D, Jimenez R, Patrick DL, Ornelas I, Bishop S, Scheel JR, Thompson B. Multilevel Intervention Raises Latina Participation in Mammography Screening: Findings from inverted exclamation markFortaleza Latina! *Cancer Epidemiol Biomarkers Prev.* 2016;25(4):584-592.
57. Raudenbush SB, AS; Cheong, AS. *HLM 7: Hierarchical linear and nonlinear modeling*. Lincolnwood, IL: Scientific Software International; 2011.
58. Bryk AS, Raudenbush SW. *Hierarchical linear models: Applications and data analysis methods.* Thousand Oaks, CA: Sage Publications, Inc.; 2002.
59. Skrondal AR-H, S. *Generalized latent variable modeling: multilevel, longitudina, and structural equation models.* Boca Raton, FL: Chapman & Hall; 2004.
60. Freund KM, Battaglia TA, Calhoun E, Darnell JS, Dudley DJ, Fiscella K, Hare ML, LaVerda N, Lee JH, Levine P, Murray DM, Patierno SR, Raich PC, Roetzheim RG, Simon M, Snyder FR, Warren-Mears V, Whitley EM, Winters P, Young GS, Paskett ED. Impact of patient navigation on timely cancer care: the Patient Navigation Research Program. *J Natl Cancer Inst.* 2014;106(6):dju115.
61. Localio AR, Berlin JA, Ten Have TR, Kimmel SE. Adjustments for center in multicenter studies: an overview. *Ann Intern Med.* 2001;135(2):112-123.
62. Kish L. *Survey Sampling.* New York: John Wiley; 1965.

63. Vierron E, Giraudeau B. Sample size calculation for multicenter randomized trial: taking the center effect into account. *Contemp Clin Trials.* 2007;28(4):451-458.
64. Vierron E, Giraudeau B. Design effect in multicenter studies: gain or loss of power? *BMC Med Res Methodol.* 2009;9:39.
65. Hade EM, Murray DM, Pennell ML, Rhoda D, Paskett ED, Champion VL, Crabtree BF, Dietrich A, Dignan MB, Farmer M, Fenton JJ, Flocke S, Hiatt RA, Hudson SV, Mitchell M, Monahan P, Shariff- Marco S, Slone SL, Stange K, Stewart SL, Strickland PA. Intraclass correlation estimates for cancer screening outcomes: estimates and applications in the design of group-randomized cancer screening studies. *Journal of the National Cancer Institute. Monographs.* 2010;2010(40):97-103.
66. Donner A, Klar N. *Design and analysis of cluster randomization trials in health research.* London: Arnold; 2000.
67. Demidenko E. Sample size determination for logistic regression revisited. *Statistics in Medicine.* 2007;26:3385-3397.
68. Hsieh F, Block D, Larsen M. A simple method of sample size calculation for linear and regression. *Statistics in Medicine.* 1998;17:1623-1634.
69. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA, Sculpher MJ, Trikalinos TA, Russell LB, Siegel JE, Ganiats TG. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA.* 2016;316(10):1093- 1103.
70. Smith DH, Feldstein AC, Perrin N, Rosales AG, Mosen DM, Liles EG, Schneider JL, Lafata JE, Meyers RE, Glasgow RE. Automated telephone calls to enhance colorectal cancer screening: economic analysis. *Am J Manag Care.* 2012;18(11):691-699.
71. Bureau of Labor Statistics. *National occupational employment and wage estimates.* Bureau of Labor Statistics; 2013.
72. Meenan RT, Stevens VJ, Hornbrook MC, La Chance PA, Glasgow RE, Hollis JF, Lichtenstein E, Vogt TM. Cost-effectiveness of a hospital-based smoking cessation intervention. *Med Care.* 1998;36(5):670-678.
73. Hoch JS. Improving efficiency and value in palliative care with net benefit regression: an introduction to a simple method for cost-effectiveness analysis with person-level data. *J Pain Symptom Manage.* 2009;38(1):54-61.
74. Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. *Health Economics.* 2002;11(5):415-430.
75. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ.* 1999;18(3):341-364.
76. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ.* 2001;10(8):779-787.
77. Diehr P, Yanez D, Ash A, Hornbrook M, Lin DY. Methods for analyzing health care utilization and costs *Annual Review of Public Health.* 1999;20:125-144.
78. Briggs A, Gray A. The distribution of health care costs and their statistical analysis for economic evaluation. *Journal of Health Services Research and Policy.* 1998;3(4):233-245.
79. Briggs A, Nixon R, Dixon S, Thompson S. Parametric modelling of cost data: some simulation evidence. *Health Econ.* 2005;14(4):421-428.
80. Baser O, Gardiner JC, Bradley CJ, Yuce H, Given C. Longitudinal analysis of censored medical cost data. *Health Econ.* 2006;15(5):513-525.
81. Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M, Orlewska E, Watkins J, Trueman P. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis. *Value Health.* 2007;10(5):336-347.
82. Clayton DC, J. Multivariate genealisations of the propotional hazards model (with discussion). *Journal of the Royal Statistical Society.* 1985;Series A(148):82-117.
83. Gutierrez R. Parametric frailty and shared frailty suvival models. *The Stata Journal.* 2002;2(1):22-44.
84. Reuland DS, Brenner AT, Hoffman R, McWilliams A, Rhyne RL, Getrich C, Tapp H, Weaver MA, Callan D, Cubillos L, Urquieta de Hernandez B, Pignone MP. Effect of Combined Patient Decision Aid and Patient Navigation vs Usual Care for Colorectal Cancer Screening in a Vulnerable Patient Population: A Randomized Clinical Trial. *JAMA Intern Med.* 2017 May 15. [Epub 2017 May 15]
85. Pelto DJ, Sly JR, Winkel G, Redd W, Thompson HS, Itzkowitz SH, Jandorf L. Predicting Colonoscopy

Completion Among African American and Latino/a Participants in a Patient Navigation Program. *J Racial Ethn Health Disparities.* 2015;2(1):101-111.
86. Horne HN, Phelan-Emrick DF, Pollack CE, Markakis D, Wenzel J, Ahmed S, Garza MA, Shapiro GR, Bone LR, Johnson LB, Ford JG. Effect of patient navigation on colorectal cancer screening in a community-based randomized controlled trial of urban African American adults. *Cancer Causes Control.* 2015;26(2):239-246.
87. McClelland GH, Judd CM. Statistical difficulties of detecting interactions and moderator effects. *Psychol Bull.* 1993;114(2):376-390.
88. Aguinis H, Beaty JC, Boik RJ, Pierce CA. Effect size and power in assessing moderating effects of categorical variables using multiple regression: a 30-year review. *J Appl Psychol.* 2005;90(1):94-107.
89. Denzin N, Lincoln Y. *The Sage Handbook of Qualitative Research.* Thousand Oaks, CA: Sage Publications, Inc.; 2011.
90. Strauss A, Corbin J. *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory.* Vol Third Edition. Thousand Oaks, CA: Sage Publications, Inc.; 2008.
91. Patton MQ. *Qualitative research and evaluation methods.* Vol Third Edition. Thousand Oaks, CA: Sage Publications, Inc.; 2002.
92. Bernard HR, Ryan GW. *Analyzing qualitative data: systematic approaches.* Los Angeles [Calif.]: SAGE; 2010.
93. Strauss A, Corbin J. *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory.* Thousand Oaks, CA: Sage; 2008.
94. Ginger.io. Big Data, Better Health. 2015. https://ginger.io/. Accessed 2/2/2015