Predicting and Addressing Colonoscopy in Safety Net Settings (PRECISE) Protocol

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1. Protocol Title

The Predicting and Addressing Colonoscopy in Safety Net Settings (PRECISE)

2. Objectives

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.

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.

Minority Supplement: A supplement for this study was awarded on 9/23/2020 to assess gastroenterology (GI) practice changes due to the COVID19 pandemic. This work will not alter the study design, number of study participants, or consent considerations.

> Specific Aim #1: Characterize organizational characteristics of GI practices
> Specific Aim #2: Apply novel analytic techniques to identify GI practice characteristics associated with timely follow-up colonoscopy completion

Supplement work is estimated to be finished by the end of 2023, which overlaps with the project period of the PRECISE study.

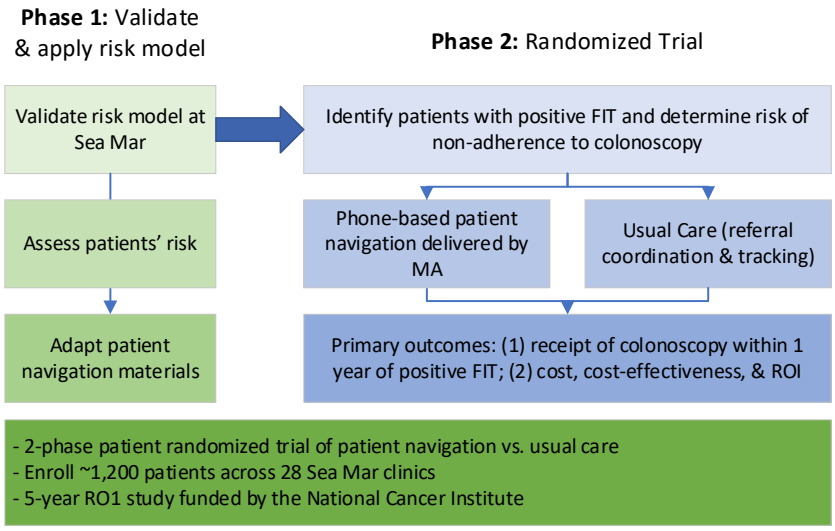
3. Background

Many patients with positive fecal tests forgo colonoscopies. 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.** 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. 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] Despite this promising research, almost all available studies have focused on *initial* CRC screening, rather than *follow-up* colonoscopy. **Despite promise, more information is needed to best target patient navigation resources.** 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 (FIT), 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. 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] While risk-prediction models hold promise for identifying patients who are likely to forgo colonoscopy, previous research on this topic is scarce. 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 (CRC Risk).

4. Study Design

Overview. This study will increase follow-up colonoscopy rates in large numbers of diverse patients by testing a patient navigation program with patients 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. **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 ~1200 patients 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 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.



5. Study Population

a. Number of Subjects

All analysis will only include patients from the SeaMar Community Health Centers. First, a retrospective analysis of patients in the past 5 years will be analyzed to create the risk model to predict failure to follow-up to a colonoscopy. Then, 1200 patents will be included in the RCT. Our study will also recruit patients and clinic staff for qualitative interviews at participating clinics within the FQHC.

b. Inclusion and Exclusion Criteria

For all aspects of the study, we will only be including patients aged 50-76 with a positive FIT test. Some exclusions may apply based on appropriateness of screening (i.e. if they had prior colorectal cancer, or are on hospice or dialysis).

This intervention is part of clinical care. Subjects may refuse colonoscopy as part of clinical care, but will have opportunity to opt out of the study.

c. Vulnerable Populations

This study will not include children or neonates by design (aged 50-76). Prisoners were not knowingly included in the cohort. Pregnant women were not targeted but may have been included incidentally. Decisionally impaired adults will not be excluded as CRC screening is recommended for these patients.

d. Setting

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.

All analysis will be conducted at KPNW. SeaMar (#FWA00000701) and Portland State University (#FWA00003920) will cede IRB oversight to the KPNW IRB (FWA 00002344).

e. Recruitment Methods/Data Collection

Retrospective Risk Model

For the retrospective risk model, patients who are aged 50-75, and have had an abnormal FIT test will be identified for the last 5 years. The risk model will identify clinical, lab, encounter, and demographic characteristics to predict those unlikely to undergo colonoscopy. The analysis of the abnormal FIT patients over the past 5 years may include more than 6,000 patients.

Patient Navigation

We will conduct a large-scale, targeted, patient-randomized controlled trial that will include ~1200 patients at 28 Sea Mar clinics. Patients will have to be 50-75 years old, and have an abnormal fecal test (FIT). We will compare rates of follow-up colonoscopy completion in ~1200 patients having either a moderate or low risk of colonoscopy adherence who are randomized to receive either a telephone-based (including text messages for scheduling, reminders, and outreach for "difficult to reach" patients) program of patient navigation delivered by trained clinical staff or usual care. Patients will be randomized based on county of their assigned clinic. Patients will be randomized using a stratified approach that considers county. The randomization will result in 600 patients assigned to the patient navigation arm and 600 assigned to the usual care arm.

All navigation and usual care will be conducted by the clinical teams at SeaMar (nurses, MA's, providers, etc.). The patient navigator will undergo intensive training during the startup phase of the study. The navigator will receive coaching (quality assurance supervision) by KPCHR study staff. Coaching will include routine (daily/weekly) check-in phone calls, and listening in on patient navigation calls and tracking navigation fidelity. KPCHR staff will continue to monitor patient navigation calls throughout the trial as part of the intervention fidelity assessment. The patient navigator will help patients address and resolve barriers to follow-up care, such as, transportation barriers through ride-share services or medical transport services.

We will assess rates of colonoscopy receipt by probability 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.

Patient Interviews: Qualitative interviews will be conducted with patients recruited through the participating clinics during the study. All recruitment materials will be approved by the IRB. Interviews will be conducted over the phone or in person by a CHR qualitative research specialist and take place at a convenient time and location for participants. We will work with the FQHC to develop recruitment materials. The decision was made to have CHR staff recruit patients and conduct interviews. However, recruitment letters will be printed on FQHC letterhead. If CHR staff encounter any challenges recruiting participants for these interviews, FQHC staff will assist with recruitment. Patient interviews completed over the phone will require a waiver of *signed* informed consent.

Clinic Staff Interviews: Select clinic personnel, some of whom may participate in Patient Navigation, will be invited to participate in a 30-60-minute phone or in person interview about project implementation. We will work with clinics to determine the most appropriate way to invite their staff to participate - this may be done via email or mailed letter. Participants will receive a $20.00 gift card for their time. Staff will be informed of the nature of the risks and benefits of participation, that participation is strictly voluntary, and that refusal to participate will not affect their employment. We will conduct our recruitment to counter coercion by emphasizing the voluntary nature of participation. Given the non-personal nature of the interview questions, we request a waiver of *signed* informed consent.

Gastroenterologist Interviews: Select GI clinic personnel and providers will be invited to participate in a 30-60-minute phone or in person interview about project implementation. We will work with clinics to determine the most appropriate way to invite their staff to participate - this may be done via email or mailed letter. Participants will receive a $25.00 gift card for their time. Staff will be informed of the nature of the risks and benefits of participation, that participation is strictly voluntary, and that refusal to participate will not affect their employment. We will conduct our recruitment to counter coercion by emphasizing the voluntary nature of participation. Given the non-personal nature of the interview questions, we request a waiver of *signed* informed consent.

f. Consent Process

For the risk model, the study only involves retrospective data, and it is not practicable to collect the data we need if we have to contact each individual to get permission. We believe this poses minimal risk.

This project will promote colorectal cancer screening through standard clinical modalities. Thus, it is an extension of usual clinical practice. Moreover, this is a pragmatic trial, and obtaining consent would unnaturally restrict our study sample, diminishing the external validity of our findings. Therefore, we request a full waiver of informed consent for the study and the reminders.

For the qualitative interview component of this study, we request a waiver of *signed* informed consent. The interviews with patients and clinic staff will use an informed consent procedure, but without signed documentation. We will give participants the option of completing the interview, and if they agree they will be interviewed over the phone or in person. Those completing the phone interview will give verbal consent. This research does not involve procedures for which written consent is normally required outside of the research context. Information about consent will be provided orally or in writing, and will include all required and appropriate additional elements of consent. This study presents no more than minimal risk of harm to subjects.

Non-English Speaking Subjects

The clinical team will be conducting the interventions and usual care, and will therefore provide the standard of care acceptable in the clinic.

All Spanish qualitative interviews will be conducted by a bilingual qualitative researcher. Patient facing materials, such as the consent form, will be provided in Spanish. See above regarding consent process.

Translations will be completed by Jennifer Rivelli, Katherine Vaughn and Natalia Tommasi, KP certified CHR staff. Jennifer, Katherine and Natalia certify that the outlined study documents below have been translated into Spanish and/or Russian to the best of their abilities as certified translators since 2012-2013 (2018 Katherine). They certify that the referenced documents have been accurately translated into Spanish and/or Russian and have retained the authentic content of the original documents.

Translated study documents submitted to the IRB for review:

- Patient recruitment introduction letter (English, Spanish, Russian)

- Phone script navigation (English, Spanish)
- Patient text messages (English, Spanish)
- Colon Cancer Fact Sheet (English, Spanish, Russian)
- Colonoscopy Bowel Prep Information Sheet (English, Spanish, Russian)
- Patient Navigation Outline Information Sheet (English, Spanish, Russian)
- Patient interview recruitment introduction letter (English and Spanish)
- Navigator Script Patient Interviews (English and Spanish)
- Patient Interview Thank You Letter (English and Spanish)
- Consent_Patient Interview (English and Spanish)

HIPAA Privacy Rule Authorization – if study will use or disclose Protected Health Information (PHI)

We request a full waiver of the privacy rule authorization requirement to allow members of the KP workforce within the KP region to use Protected Health Information (PHI) from Seamar. For the qualitative interview component of this study, we request an alteration of the privacy rule authorization - participant signature and date cannot be obtained.

Electronic medical records (EMRs) at participating clinics will be used to identify the retrospective data and a prospective cohort of potential study participants based on inclusion and exclusion criteria. Electronic medical records (EMRs) will also be used to look for outcomes (completed FIT/FOBT or colonoscopy). We will run analyses on the control vs. intervention patients to determine if our intervention had a significant effect. A CHR auditor will access clinical data from the participating sites to inspect the quality and ensure the accuracy of the data. Data from all sites will be gathered at the clinics and sent via secure file transfer to CHR for analysis. Data Use Agreements will be established to 1) allow for the aforementioned transfer, and 2) to permit CHR to send analyzed limited datasets back to the clinics for further refinement on any issues encountered. PHI will not be shared when the data are sent back for further validation/refinement.

Use of the medical record by clinic staff is regular clinical practice, required to identify participants for the overall study. Therefore, we would be unable to seek authorization prior to using the medical record. Only the PHI data required to identify the study population will be accessed. However, we may also: 1) access additional patient information such as sociodemographic characteristics that may be related to differences in program reach and effectiveness, and 2) access the minimum PHI necessary to properly carryout the research task of interviewing patients. (Use of the medical record is also required to identify participants for qualitative interviews, so we would not be able to seek signature and date for authorization prior to using the medical record.) The use and disclosure of PHI will involve no more than minimal risk to the privacy of individuals. All identifiable study data will be stored within clinic data systems. See *Section 8. Privacy, Confidentiality, and Data Security* below for more information.

6. Study Procedures

This study will test a predictive risk model and patient navigation. In Phase I we will validate a current predictive model in the SeaMar setting and our ability to assess the patients probability of adherence to colonoscopy. In addition, we will be adapting the patient navigation program materials based on local resources, develop the patient navigator protocol and train patient navigators. The study will also include qualitative interviews with patients and clinic staff.

In Phase II, we will conduct a patient-randomized trial that tests the effectiveness of patient navigation. Both phases will be guided by an advisory group of clinicians, researchers, policy makers, and patients.
The participating clinics will be federally qualified health centers (FQHCs) that serve populations that speak several languages, but mostly English or Spanish. Materials will be translated by Jennifer Rivelli and Natalia Tommasi, KP certified CHR staff.

As part of the minority supplement work, Dr. Cynthia Mojica will conduct semi-structured in-depth interviews (in-person, phone or virtual platform) with GI providers or office staff (including clinic mangers and colonoscopy schedulers) to assess practice changes due to the COVID19 pandemic. (These interviews are distinct from the GI interviews described above on page 4 of the protocol.) Interviews will be recorded and last about 30-60 minutes. Respondents will be offered a $25 gift card as a token of appreciation for their time. Given the non-personal nature of the interview questions, we request a waiver of *signed* informed consent.

This study does not involve genetic testing or collection of genetic information.

7. Data Analysis

a. Analysis Plan

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. We will follow best practices and be guided by previous economic analyses of patient navigation for CRC screening follow-up. 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 varying 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.

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.

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 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.

Minority Supplement:

For minority supplement aim 1, we will use descriptive statistics to summarize the structural characteristics and processes of GI practices.

For minority supplement aim 2, we will use data gathered from aim 1 to conduct a configurational analysis. We will use configurational comparative methods (CCMs) to identify conditions (organizational structures, processes, and

policies, and changes in processes and policies) associated with follow-up colonoscopy completion rate and time to colonoscopy completion among Sea Mar Community Health Center patients.

b. Sharing of Results with Subjects

Test results will be shared with subjects per standard clinical practice. We will also publish findings and share findings with the participating clinics.

c. Data and Specimen Banking – N/A

8. Privacy, Confidentiality, and Data Security

To reduce any risk of disclosure of confidential information, subjects' privacy and confidentiality will be assured by:

a. Securely storing data in password-protected files and directories on staff computers within firewall protected networks;
b. Removing or obscuring participant names prior to any presentation, publication, or other sharing of data outside the research team, except with the expressed written consent of the subject(s);
c. Ensuring that unmodified data (containing identifying data or features) are accessible only to members of the research team working under the direction of the investigators for the duration of the project; identifiers will be removed as soon as is feasible;
d. Transporting interview materials in locked containers.

9. Provisions to Monitor the Data to Ensure the Safety of Subjects

a. Designation of a Data Safety Monitor:
An independent investigator will serve as an Independent Monitor for Data and Safety for the project. S/he will not be key personnel in this grant. S/he will be qualified to review the patient safety data generated by this study because of their unique clinical and research expertise.

b. Safety Review Plan and Protocol for Identifying, Reviewing and Reporting Adverse Event to IRB and NIH:
Study progress and safety will be reviewed semi-annually (and more frequently if needed). Progress reports, including patient recruitment and Adverse Events (AEs) will be provided to the Independent Monitors following each of the semi-annual reviews. A semi- annual report will be compiled and will include a list and summary of AEs. In addition, the report will address (1) whether AE rates are consistent with pre-study assumptions; (2) and the status of follow-up to abnormal screening results (within 6 months). The annual report will be sent to the Independent Monitor, and will be forwarded to the IRB and NIH, if applicable. The IRB and other applicable recipients will review progress of the study on an annual basis.

The PI will meet with the project director and research staff weekly. All AEs and unanticipated problems occurring during the study will be collected, documented, and reported to the PI and the Independent Monitor immediately. During the intervention phase of the study, clinic staff will report any AEs or unanticipated problems that may have occurred during the intervention.

c. Assessment of external factors that may impact participant safety and/or ethics for the research study:
The PI will continue to follow-up with new information in the literature and results of related studies. If any new information is available that would impact the relevance of the study, it will be documented and reported to the Independent Monitor by email or phone.

d. Advanced plans for interim and/or futility analysis:
Interim analysis of data will not be conducted as part of this study. Given our goal of evaluating the implementation and maintenance of this evidence-based intervention, an interim analysis would be impractical. We do not anticipate that new data would show trends for negative outcomes resulting from the proposed interventions.

10. Risks and Benefits

a. Risks to Subjects

The minimal risks to subjects appear reasonable when weighed against the potential societal benefit. This study proposes to increase colorectal cancer screening, which is beneficial to the subjects, and increases recommended screening.

b. Potential Benefits to Subjects

Participants of the study and qualitative interviews, are not expected to directly benefit from participating, other than the possible benefit of increasing recommended screening, potentially finding cancers earlier than if not screened, and feeling positive about contributing to the research itself.

11. Costs to Participants

The proposed intervention will be of no cost to the patient.

12. Compensation to Participants

Clinics will participate under a clinic impact fee, and patients may receive a $20 gift card for their participation in the interviews.

13. Resources Available

Our study will use Patient Navigation to engage patients in completing their screening. Our study team will include trained Patient Navigation and will use their expertise to adapt material and define intervention components.

14. Drugs or Devices

N/A

15. Multi-Site Coordination

This site will be the IRB of record for SeaMar Community Health Centers (#FWA00000701), which will cede to the KPNW IRB (FWA 00002344).

16. Community-Based Participatory Research

We will use proven community based participatory (CBPR) approaches throughout the design, execution, and dissemination of the trial. We will apply novel and locally designed approaches, such as patient navigation and continue to partner with our established advisory board to solicit and incorporate patient and clinic feedback throughout each phase of the research study. Community research partners will be required to complete all necessary human subjects' protection training.

Protocol Modifications

Original Plan	Modification
PN intervention will be overlaid on usual care	Usual care includes a call from care coordinators, navigated patients will not receive usual care
Navigator will be nurse-trained	Navigator will have clinical experience, but not be a nurse
Patients in highest probability quintile will not be randomized into the study (will receive surveillance)	All patients (across probability strata) will be randomized, and effectiveness of navigation will be assessed by quintile
Eligibility criteria: FIT positive plus referred	Eligibility criteria: FIT positive and referred and reviewed by clinic champion/GI (to reduce post-randomization drop out, randomized in error)
Final outcome determination: Medical record review	Final outcome determination: Medical record review plus records request to GI and blinded adjudication
Cost analysis, timeline w/o pandemic interruptions	Eliminate the cost-analysis activities to extend our recruitment interval to get closer to reaching our 1200-patient goal