Cover Page

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Comparative Effectiveness Pilot Trial of Mailed Cologuard Outreach to Mailed FIT Outreach

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PROTOCOL

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Executive Summary/Abstract

Colorectal cancer (CRC) accounts for 8% of cancer incidence and 9% of cancer-related mortality in the United States (US). About 11% of CRC cases are diagnosed before age 50—known as early age onset CRC (EOCRC)—with incidence and mortality rates increasing 1.6% and 1% per year between 2005-2014, and an unequal burden among Asian, American Indian/Alaska Native, Black and Hispanic racial/ethnic groups and those with Medicaid or uninsured. The increasing EOCRC burden informed a US Preventive Services Task Force (USPSTF) recommendation to initiate CRC screening among average risk adults starting at age 45, rather than 50. This recommendation would expand CRC screening to 21 million Americans, with 4 million more turning 45 each year. There is a lack of evidence to inform how to optimize impact of CRC screening among adults ages 45-49. Specifically, there are three critical knowledge gaps: 1) we lack information regarding acceptability of CRC screening among those ages 45-49 and have not investigated factors that might influence CRC screening uptake among this newly eligible population, 2) there are concerns that CRC screening disparities that exist among adults ages ≥50 are likely to emerge in this younger age group without a targeted screening strategy and 3) it is unclear whether this age group will respond to current CRC screening practice or more active outreach.

The central objective of this proposal is to develop a targeted CRC screening strategy among adults ages 45-49 to maximize screening uptake and prevent cancer disparities. Our study will recruit adults ages 45-49 receiving care within a large health system to answer these questions. First, we will conduct interviews with screening-eligible adults and providers responsible for CRC screening referral and coordination regarding factors influencing CRC screening uptake (Aim 1). We will then characterize the acceptability of CRC screening by conducting a pilot trial to establish feasibility of a larger trial (Aim 2) and to highlight effective strategies for implementing screening among adults ages 45-49. Our long-term goal is to use these pilot data to inform a randomized controlled trial of the comparative effectiveness of an active outreach strategy including mailed

multitarget stool DNA (mt-sDNA; Cologuard) test versus mailed fecal immunochemical test (FIT) for optimizing uptake and preventing emergence of CRC screening disparities.

Our central hypothesis is that a targeted CRC screening strategy will lead to higher screening uptake. To complete this study, we will leverage electronic health record data and primary data from average risk adults ages 45-49 receiving care at University of California, San Diego Health System (UCSDHS). We plan to include adults ages 45-49 receiving care at UCSDHS, with an assigned primary care provider (PCP) at UCSDHS, currently not up to date with CRC screening and without prior colonoscopy or personal history of inflammatory bowel disease, polyps or CRC. For interviews, we will recruit eligible adults ages 45-49 and providers to answer questions about potential patient-, provider- and system-related factors relevant to CRC screening uptake specific to adults ages 45-49. Our pilot trial intervention will be mailed multi-target stool DNA test outreach, which in survey data has been found to be preferable in individuals under age 50 when offered a choice of screening tests. The pilot trial control group will be mailed fecal immunochemical test outreach, which has been proven highly effective at increasing screening uptake, particularly among underserved populations. Equipoise exists as to the best approach for offering CRC screening outreach, because both of these tests are guideline recommended for screening but have not been compared head-to-head in a randomized trial to determine whether offering one strategy may be superior to the other. Our primary trial outcome is completion of CRC screening using any USPSTF-recommended modalities within 3 months of date of randomization.

Our study will be the most comprehensive examination of early CRC screening initiation in the US to date and will provide context to the updated CRC screening policy and a potential framework for wider implementation of earlier CRC screening in adults ages 45-49.

Introduction and Background

A. Introduction

1. Colorectal cancer is a growing public health problem burden among adults ages <50.

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States (US), with 11% of cases diagnosed before age 50—known as early age onset CRC (EOCRC).[1] CRC risk increases with age and disproportionately affects men, Black and American Indian and Alaska Native (AI/AN) racial/ethnic groups and persons with limited healthcare access or low socioeconomic status (SES).[2–5] While CRC incidence and mortality have decreased in adults ages ≥50, EOCRC incidence and mortality have increased steadily.[6] By 2030, an estimated 10% of colon and 22% of rectal cancers will be EOCRC cases, making preventive strategies and earlier CRC detection crucial.[7] CRC screening is seen as a major driver of decreases in CRC incidence and mortality in adults ages ≥50.[6,8] The rising EOCRC morbidity and mortality burden and the evidence among adults ages ≥50 of CRC screening efficacy were the impetus for the recent US Preventive Services Task Force (USPSTF) recommendation to initiate CRC screening in average risk adults at age 45 rather than 50.

2. USPSTF updates assume perfect screening participation despite imperfect uptake.

The significant update to the USPSTF CRC screening guidelines is mainly supported by cancer screening modeling which assumes perfect participation in screening. These models predicted earlier CRC screening at 45 could prevent up to 3 additional CRC cases and 2 CRC deaths and lead to 15-34 life-years gained per 1000 persons screened.[9] While USPSTF projections of potential benefit rely on prior screening studies in adults ages ≥50, the modeling additionally assumes 100% participation in screening to calculate predicted benefits.[10,11] This assumption is problematic, as only 68% of US adults ages 50-75 are up-to-date with CRC screening, with only 48% of adults ages 50-54 reporting being up-to-date, and early evidence of CRC test prevalence among adults ages 45-49 only reaching 21%.[1,12–14] In addition to age-related

disparities, disparities by sociodemographic groups are profound—including in Black (65%), Hispanic (59%), AI/AN (59%) and Asian adults (55%) compared to White adults (69%) and those insured via Medicaid (54%) compared to other insurance (74%)—which is correlated with later stage at CRC detection and lower CRC-related survival.[1,15,16] While the USPSTF recommendation notes there is sufficient evidence to recommend earlier CRC screening, this assumption of perfect uptake highlights limited empirical evidence of CRC screening uptake among adults ages 45-49. Data on screening uptake in this newly eligible population are needed to understand whether the benefits estimated by the USPSTF can be attained and whether disparities and inequities in screening and CRC outcomes currently observed among adults ages 50-75 will emerge in adults ages 45-49.

3. Strong need to learn about factors influencing screening uptake in adults ages 45-49.

To ensure the greatest benefits of CRC screening among adults ages 45-49, it is imperative to maximize CRC screening uptake and learn about factors influencing uptake. Given the current screening levels among adults ages 50-75 years, the assumption of 100% screening uptake in adults ages 45-49 does not reflect real-world screening uptake. Developing a strategy that maximizes uptake in this population is necessary to reach the USPSTF model benefit estimations. Such a strategy could also prevent screening disparities from developing, thus improving CRC-related outcomes.

Among individuals ages 50 and older, studies have found the fecal immunochemical test (FIT), particularly when mailed to patients with directions and reminders, to have wider acceptability compared to colonoscopy.[17–19] Multi-target stool DNA testing (Cologuard) could be similarly or even more effective, given its direct-to-patient mailing of the test, personalized customer service that includes facilitation and reminders for test completion, high sensitivity for finding cancers (93% vs. 74% for FIT), and only requiring follow-up every three years for a normal finding, rather than yearly. Additionally, non-randomized studies among adults older than 50 report participation rates that are higher than typically achieved with mailed FIT outreach.[20] Thus at present, while it

is clear that mailed FIT outreach is the most evidence based intervention for increasing screening participation among individuals older than 50, survey data suggest that individuals under age 50 may prefer testing with Cologuard, and use of Cologuard may have advantages over FIT in terms of sensitivity for CRC and need for less frequent use. In addition, it is unclear who in this newly eligible age group is most likely to screen, and what might motivate them to undergo CRC screening. The relevance of factors affecting screening uptake, such as prior knowledge,[21–23] psychosocial[23–26] and sociocultural factors,[21,24,27–29] and access to care,[23,27,29–32] are unknown, hampering the ability to appropriately target these newly eligible adults. Addressing these knowledge gaps is necessary to maximize screening uptake and prevent extension of age, socioeconomic status, and racial/ethnic disparities observed in adults over 50 to those ages 45-49.

Study Hypotheses and Objectives

A. Primary Objective and Hypothesis

The primary study objective is to identify an optimal CRC screening outreach strategy for adults ages 45-49 that maximizes uptake and minimizes disparities and inequities. The primary study hypothesis is that, compared to usual care mailed FIT outreach, outreach with mt-sDNA (Cologuard) will lead to higher screening uptake among adults ages 45-49.

B. Aims and Aim-Specific Hypotheses

Aim 1. Interview participants and providers about factors influencing CRC screening uptake.

Hypothesis: Patient risk perception and lack of patient and organizational EOCRC risk education will be identified as influential CRC screening factors.

Aim 2. Conduct pilot trial of comparative effectiveness of mailed Cologuard outreach vs. mailed FIT outreach screening strategies among adults ages 45-49 to establish feasibility of larger trial.

Hypothesis: Findings from the pilot will show conducting a full RCT is feasible, help to refine the outreach strategy implemented, and inform final power and sample size estimates.

Summary of the Study Design

This study employs a mixed methods design to develop a CRC screening strategy for adults ages 45-49. First, our study will employ interviews of pilot trial participants and providers involved in CRC screening referral and coordination to qualitatively examine factors influencing CRC screening uptake. In parallel, we will conduct a pilot randomized controlled trial to compare a mailed multi-target stool DNA test (Cologuard) outreach strategy to mailed fecal immunochemical test (FIT) outreach. Results from our interviews and the pilot trial will inform a larger, fully powered trial of Cologuard outreach vs. mailed FIT outreach for CRC screening.

A. Study Rationale

We chose to pursue this mixed methods design to simultaneously learn about factors at the patient, provider and system levels that might influence CRC screening uptake and examine the potential acceptability of a mailed Cologuard outreach strategy compared to mailed FIT outreach. The trial will enable us to conduct a real-world examination of potential uptake of CRC screening among adults ages 45-49, where evidence regarding CRC screening is currently limited.

We choose to test the mailed Cologuard outreach strategy as the primary pilot intervention because of its demonstrated efficacy among adults ages 50-75, and potentially greater acceptability as a screening modality compared to other available tests.[33] The control group will receive mailed FIT outreach, a strategy proven effective at increasing CRC screening uptake among individuals not up to date with screening.[34,35] This control arm reflects a proven screening outreach strategy that has been implemented in many settings, including at University of California San Diego Health System.

We acknowledge that some adults ages 45-49 might be more inclined to utilize other screening modalities, such as colonoscopy. Thus, we are measuring screening uptake as an outcome of our study, to include any potential screening modality used as covered by the USPSTF guidelines. Our decision to consider any potential screening modality uptake as completed

screening is based on the ultimate goal of the study to maximize screening among this newly eligible screening population.

B. Study Population and Rationale

Aim 1. Interviews

The specific inclusion criteria for Aim 1 are:

Patient Participants

- Adults ages 45-49.
- EHR documentation indicating the patient has an assigned primary care provider at UCSDHS
- ≥1 UCSDHS health visit within the last year
- Lives within San Diego or Imperial County (via Residential Zip Code)
- Currently not up to date with CRC screening
- Insured by private health insurance, public health insurance (i.e., Medicaid [Medi-Cal]) or other health insurance

Provider Participants

- Physicians or Advanced Practice Providers (i.e., Nurse Practitioners and Physician Assistants) involved in referral to CRC screening. Providers eligible for participation in this study will include those who practice in the following specialties:
    - Primary Care
    - Obstetrics/Gynecology
    - Gastroenterology
    - Oncology

The specific exclusion criteria for Aim 1 are:

Patient Participants

- Up to date with CRC screening, including:

    - Colonoscopy within past 9.5 years
    - Sigmoidoscopy within the past 5 years
    - CT colonography within the past 5 years
    - gFOBT or FIT in the past 10 months
    - Stool DNA test within the past 3 years
- Prior history of colonic disease including:
    - Inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease)
    - One or more colorectal neoplastic polyps (i.e., adenomas)
    - Colorectal cancer
- Prior colectomy
- Lack of health insurance

Provider Participants

- Less than 1 year practice experience at UCSDHS

Aim 2. Pilot Trial

The specific inclusion criteria for Aim 2 are:

- Adults ages 45-49
- EHR documentation indicating the patient has an assigned primary care provider at UCSDHS
- ≥1 UCSDHS health visit within the last year
- Lives within San Diego or Imperial County (via Residential Zip Code)
- Currently not up-to-date with CRC screening
- Insured by private health insurance, public health insurance (i.e., Medicaid [Medi-Cal]) or other health insurance

The specific exclusion criteria for Aim 2 are:

- Up-to-date with CRC screening, including:

    - Colonoscopy within past 9.5 years
    - Sigmoidoscopy within the past 5 years
    - CT colonography within the past 5 years
    - gFOBT or FIT in the past 10 months
    - Stool DNA test within the past 3 years
- Prior history of colonic disease including:
    - Inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease)
    - One or more colorectal neoplastic polyps (i.e., adenomas)
    - Colorectal cancer
- Prior colectomy
- Lack of health insurance

1. Identification of Candidate Patients and Recruitment.

Aim 1. Interviews

To conduct the interviews outlined in Aim 1, we will use the UCSDHS electronic health record (EHR) to identify individuals ages 45-49 receiving UCSDHS care and not up-to-date with CRC screening to participate. We will require verbal consent for their participation and seek waiver of written documented consent on the grounds that 1) the research does not meet the California definition of a medical experiment, 2) the research presents no more than minimal risk or harm to participants and involves no procedures for which written consent is normally required outside of the research context, and 3) the participant will be presented all of the required elements of consent in written format prior to conducting the research. For interviews with provider participants, we will also require verbal consent for participation and seek waiver of written documented consent for the same reasons noted above. If we do not receive an adequate number of interview responses from trial participants or provider participants, we will consider

incorporating surveys as an alternative data collection method and provide the update in a later IRB modification.

Aim 2. Pilot Trial

For the pilot trial in Aim 2, we will use the UCSDHS electronic health record (EHR) to identify and randomize individuals meeting inclusion/exclusion criteria (see page 21 and pages 43-44 for Aim 2 pilot trial randomization strategy). To identify eligible study participants for pilot trial recruitment, we request a partial waiver of HIPAA Authorization, on the grounds that only the minimum, necessary information needed for recruitment will be used, the use or disclosure of the minimum necessary PHI involves no more than minimal risk to the privacy of individuals, and the research could not practicably be initiated without waiver and without access to and use of PHI. Prior to randomization, we will seek HIPAA Authorization and documented informed consent from all potential participants in the study. Only those who provide signed HIPAA authorization and informed consent documents will proceed to randomization and study follow-up.

2. Exclusion Criteria Data Ascertainment.

We will identify relevant exclusion criteria through the UCSDHS EHR based on previously defined algorithms (**Table 1**). Prior colonoscopy (reflecting up to date CRC screening) will be identified using Current Procedure Terminology (CPT) codes. History of IBD, CRC and colorectal adenomas will be identified using International Classification of Diseases, 9th and 10th editions (ICD-9/10). We will also confirm exclusion criteria by examining problem lists and other EHR data sources (such as the EHR health maintenance registry) with structured queries.

Table 1. Study Exclusion Criteria

Exclusion Criteria	Codes
Up to Date with CRC Screening	Colonoscopy CPT: 44388-44394, 44397, 44401-44407, 45355, 45378-45393, 45398, G0105, G0121, G6019, G6020, G6024-G6025 Stool Blood Test CPT: 81528, 82270, 82274, G0328, G0464 Sigmoidoscopy CPT: 45330-45335, 45337-45338, 45346-45347, 45340-45342, 45349-45350, G0104
History of Inflammatory Bowel Disease	ICD-9: 555.9, 560.89; ICD-10: K52.9
History of Colorectal Adenomas	ICD-9: V12.72; ICD-10: Z86.010
Prior colorectal cancer	ICD-9: 153.0-153.9, 154.0-154.3, 154.8; ICD-10: C18.0, C18.2-C18.9, C19.9, C20

C. Intervention Regimens and Rationale

1. Mailed multi-target stool DNA (Cologuard) test outreach.

The intervention to be tested in the pilot is mailed Cologuard outreach, a multi-component strategy that has been proven to be a highly acceptable test among current screening-eligible adults.[35,36] Cologuard is a USPSTF-recommended at-home screening test for blood in stool that additionally examines DNA markers in the stool to detect cancer. Its sensitivity to detect CRC is 92% and specificity is 87%.[37] Abnormal Cologuard results are followed up with a colonoscopy to identify and remove pre-cancerous polyps or diagnose early-stage CRC. Dr. Samir Gupta will be the ordering provider of the Cologuard tests for those participants randomized to the mailed Cologuard outreach. Participants randomized to mailed Cologuard outreach will receive:

1) advanced notification (primer) via mail one week prior to receiving the Cologuard test;

2) Cologuard test shipped directly to patient's home, with 2 months of personalized support to facilitate screening completion included. Included with the Cologuard test is a collection kit that may be returned at no cost to the patient via UPS (either by contact-free pick-up or drop-off at UPS). The Cologuard Customer Care Center also is available via phone or chat to aid with test completion.

3) Patient results will be sent to the ordering provider within 2 weeks of test completion and return.

Patients with normal results will be sent a letter to repeat CRC screening in 3 years. Patients with abnormal results will be sent a letter encouraging follow up colonoscopy, and their primary care provider will be notified and requested to order colonoscopy. Patients with colonoscopy orders will receive usual care colonoscopy scheduling, preparation, and completion by the UCSDHS GI department. Notably, some clinicians at UCSDHS are already offering Cologuard as a usual care screening test.

2. Mailed fecal immunochemical test (FIT) outreach.

The control group to be tested in the pilot is mailed FIT outreach, a multi-component strategy found to have the largest effect size to improve CRC screening uptake compared to usual care.[35,36] FIT is a USPSTF-recommended at-home screening test for blood in stool. Abnormal FIT results are followed up with a colonoscopy to identify and remove pre-cancerous polyps or diagnose early-stage CRC.[34] FIT test kits will be prepared at UCSD Health to be delivered to participants randomized to this study arm. Participants randomized to mailed FIT outreach will receive:

1) advanced notification (primer) via mail one week prior to receiving the FIT kit;

2) FIT kit normally offered at UCSDHS (Polymedco OC Light) with study information, invitation and instructions to complete FIT and how to opt-out; and

3) reminders via mail 14 days and 28 days after FIT kit receipt.

FIT kits will be mailed to UCSD Health System to undergo current usual care assay and reporting, based on the Polymedco OC Light criteria (the current test used within UCSDHS). Patients with normal results will be sent a letter to repeat CRC screening in a year. Patients with abnormal results will be sent a letter encouraging follow up colonoscopy, and their primary care provider will be notified and requested to order colonoscopy. Patients with colonoscopy orders will receive usual care colonoscopy scheduling, preparation, and completion by the UCSDHS GI department.

D. Outcome Measures and Rationale

1. Aim 1 Interview Constructs

Interviews will focus on patient-level, provider-level and system-level constructs, which we view as interdependent, based on a prior CRC screening study by May et al. (**Figure 1**).[38] Patient factors will cover psychosocial and sociocultural factors, health literacy and behavior, perceived CRC risk and perceived screening benefits and harms. Provider factors will cover harms and benefits conferred by CRC screening and guideline knowledge and beliefs. System factors will cover access to care and new guideline implementation. Interviews will be semi-structured to offer flexibility to discuss topics of greatest interest to participants. Interviews will last approximately 45-60 minutes and be either in-person or video-based. Interview guides for trial participants and provider participants include lists of questions that could be asked within patient-level, provider-level and system-level constructs. We aim to evenly cover questions within all three constructs, such that approximately 20 minutes is devoted to each area. However, due to the semi-structured nature of the interviews, not all questions included in the interview guides will be asked of each interview participant. Questions within the interview guide are ordered based on priority to be covered within the interview.

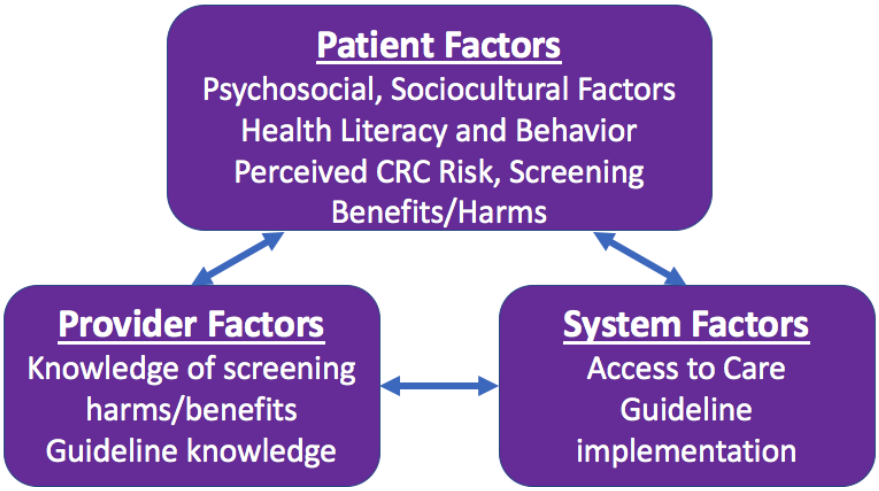

Figure 1. *Interview constructs of interest.*

2. Aim 2 Primary Outcome

We will use the Healthcare Effectiveness Data and Information Set (HEDIS) documentation to inform our CRC screening uptake variable. This variable will incorporate CPT, Healthcare Common Procedural Coding System (HCPCS), and ICD-9/10 coding to identify FIT or guaiac fecal occult blood tests (CPT: 82270, 82274; HCPCS: G0328), flexible sigmoidoscopy (CPT: 45330-45335, 45337-45342, 45345-45347, 45349, 45350; HCPCS: G0104; ICD-9: 45.24), colonoscopy (*CPT/HCPCS codes mentioned in* ***Table 1***; ICD-9: 45.22, 45.23, 45.25, 45.42, 45.43), CT colonography (CPT: 74261-74263) and FIT-DNA tests (CPT: 81528, HCPCS: G0464). We will also conduct manual EHR review to validate our HEDIS-defined algorithm.

3. Aim 2 Secondary Outcomes

In the pilot trial, we will measure multiple outcomes to assess feasibility of a larger trial. We will measure the total number of participants who opt out of participation in the pilot as a recruitment outcome. We will also measure the number of participants with undeliverable Cologuard or FIT kits, known as mail fail rate, as an intervention outcome. Number of individuals with kits that could not be processed due to collection issues (missing collection date, too much or too little sample) will be quantified for both groups. Among those with abnormal Cologuard or FIT, we will measure the proportion who are referred to colonoscopy and the proportion who complete colonoscopy via manual EHR review of participants with abnormal Cologuard or FIT results. We will conduct the manual EHR review at 3 months, 6 months, and 9 months post-randomization. If through the course of manual EHR review a patient is discovered not to have completed colonoscopy, the study team will contact the assigned primary care provider to alert them that the patient had an abnormal Cologuard or FIT and did not complete colonoscopy. The contact will be through a UCSD Epic staff message from the study team to the primary provider. If receipt of the message is not acknowledged after two staff messages, then the study team will contact the primary provider's assigned clinic staff via telephone to alert them that the patient has an abnormal Cologuard or FIT and has not received referral for colonoscopy.

E. Sample Size and Rationale

For interviews, we plan to recruit 20 adults ages 45-49, as well as 10 UCSDHS providers involved in CRC screening referral and coordination, including primary care providers, obstetricians or gynecologists, gastroenterologists and oncologists. Participants will be selected by applying a stratified random sampling method to ensure equitable representation from the five major racial and ethnic groups. Selected participants will be contacted via e-mail about the study with directions to schedule a time for their interview, if they are interested in participating. Scheduling of interviews will occur using Calendly platform, allowing patients to directly choose a time slot in the interviewer calendar based on their availability. Participants will be asked to provide their name and email address to schedule an appointment. Provider participants will be recruited via convenience sampling and contacted directly via email about the study with directions to schedule a time for their interview, if they are interested in participating. Scheduling of interviews will occur using Calendly platform, allowing patients to directly choose a time slot in the interviewer calendar based on their availability. Provider participants will be asked to provide their name and email address to schedule an appointment.

As our Aim 2 pilot trial is a feasibility study, the sample size is not projected to ensure study power for hypothesis testing. We instead assess precision of our primary outcome, CRC completion in 3 months, based on a projected sample size of 100 (50 per study group; 10 per race/ethnicity group) and a two-sided type I error alpha of 0.05. Based on this sample, we will have 80% power to detect a $\geq$15 percentage point higher rate of completion in the Cologuard group than the mailed FIT outreach group, assuming that the completion rate in the mailed FIT group is 23%. The assumption of mailed FIT completion is based on internal, UCSDHS data from prior mailed FIT outreach in 45 to 49 year olds.

Patient Population

A. Recruitment and Screening Strategy

Aim 1 Interviews

For interviews, we plan to recruit 20 adults ages 45-49 receiving UCSDHS care, as well as 10 UCSDHS providers involved in CRC screening referral and coordination, including primary care providers, obstetricians or gynecologists, gastroenterologists and oncologists. Using the UCSDHS EHR, we will conduct a query for a list of all potential patient participants who meet the eligibility criteria. We will use both Epic and Care Everywhere platforms to ascertain eligibility criteria for recruitment. Participants will be selected by applying a stratified random sampling method to ensure equitable representation from the five major racial and ethnic groups: Non-Hispanic White, Black, Hispanic, Asian/Pacific Islander, and Other. Selected participants will be contacted via e-mail about the study with directions to schedule a time for their interview, if they are interested in participating. Scheduling of interviews will occur using the Calendly platform, allowing patients to directly choose a time slot in the interviewer calendar based on their availability. Participants will be asked to provide their name and email address to schedule an appointment. Provider participants will be recruited via convenience sampling and contacted directly via email for participation and scheduling of interview in the manner described above.

We will seek verbal informed consent from patient and provider participants prior to conducting interviews. If selected participants schedule a date and time to participate in interviews, they will be provided with consent documents to review prior to conducting the interviews. If patients do not review the consent documents prior to the scheduled interview date, the interviewer will begin the interview session by going over the consent document and then asking for verbal consent. Recruitment will continue until a sample size of 20 patient participants and 10 provider participants who do not opt out of the research is achieved. If we do not receive an adequate number of interview responses from trial participants or provider participants, we will consider incorporating

surveys as an alternative data collection method and submit an IRB modification reflecting that update.

Aim 2 Pilot Trial

Using the UCSDHS EHR, we will conduct a query for a list of all potential participants who meet the eligibility criteria. We will use both Epic and Care Everywhere platforms to ascertain eligibility criteria for recruitment. Among the list of adults deemed eligible for recruitment, we will stratify individuals based on their EHR-documented race/ethnicity into one of five groups: Non-Hispanic White, Black, Hispanic, Asian/Pacific Islander, Other. From these groups, we will select a list of 20 individuals to be recruited. In sum, the 100 individuals will be comprised of 20 individuals selected at random from 5 self-reported racial/ethnic groups, with the intent that each racial/ethnic group will have 10 individuals represented in the mailed Cologuard outreach and mailed FIT outreach (each group makes up 20% of the sample in each arm). This will ensure equal balance of participants from each racial/ethnic group in each trial arm.

Eligible individuals will be mailed a postcard briefly describing the study and asking patients to scan a QR code if they are interested in participating. The QR code will take eligible individuals to eConsent forms within REDCap, where they will be provided with informed consent and HIPAA Authorization forms that will need to be completed to participate in the study. Electronically completed and signed informed consent and HIPAA authorization forms will be required prior to randomization. HIPAA Authorization is necessary to release relevant patient information to Exact Sciences, the company that will mail and implement the Cologuard test, should the participant be randomized to that group. Additionally, HIPAA Authorization ensures participant electronic health records may be examined to measure the study's outcomes of interest over the course of study follow-up.

If individuals decline participation or do not sign HIPAA authorization and informed consent documents, they will be replaced by another eligible individual from the same EHR-documented race/ethnicity grouping. After agreeing to participate, individuals within each race/ethnic group will

be assigned randomly to the mailed Cologuard outreach and mailed FIT outreach arms, such that an equal number of individuals from each group is included in each trial arm. Recruitment will continue until a sample size of 50 individuals per trial arm (mailed Cologuard outreach and mailed FIT outreach) who consent to participation in the study is achieved.

B. Inclusion and Exclusion Criteria

Aim 1. Interviews

The specific inclusion criteria for Aim 1 are:

Patient Participants

- Adults ages 45-49.
- EHR documentation indicating the patient has an assigned primary care provider at UCSDHS
- ≥1 UCSDHS health visit within the last year
- Lives within San Diego or Imperial County (via Residential Zip Code)
- Currently not up to date with CRC screening
- Insured by private health insurance, public health insurance (i.e., Medicaid [Medi-Cal]) or other health insurance

Provider Participants

- Physicians or Advanced Practice Providers (i.e., Nurse Practitioners and Physician Assistants) involved in referral to CRC screening. Providers eligible for participation in this study will include those who practice in the following specialties:
    - Primary Care
    - Obstetrics/Gynecology
    - Gastroenterology
    - Oncology

The specific exclusion criteria for Aim 1 are:

Patient Participants

- Up to date with CRC screening, including:
    - Colonoscopy within past 9.5 years
    - Sigmoidoscopy within the past 5 years
    - CT colonography within the past 5 years
    - gFOBT or FIT in the past 10 months
    - Stool DNA test within the past 3 years
- Prior history of colonic disease including:
    - Inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease)
    - One or more colorectal neoplastic polyps (i.e., adenomas)
    - Colorectal cancer
- Prior colectomy
- Lack of health insurance

Provider Participants

- Less than 1 year practice experience at UCSDHS

Aim 2. Pilot Trial

The specific inclusion criteria for Aim 2 are:

- Adults ages 45-49
- EHR documentation indicating the patient has an assigned primary care provider at UCSDHS
- ≥1 UCSDHS health visit within the last year
- Lives within San Diego or Imperial County (via Residential Zip Code)
- Currently not up to date with CRC screening

- Insured by private health insurance, public health insurance (i.e., Medicaid [Medi-Cal]) or other health insurance

The specific exclusion criteria for Aim 2 are:

- Up to date with CRC screening, including:
    - Colonoscopy within past 9.5 years
    - Sigmoidoscopy within the past 5 years
    - CT colonography within the past 5 years
    - gFOBT or FIT in the past 10 months
    - Stool DNA test within the past 3 years
- Prior history of colonic disease including:
    - Inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease)
    - One or more colorectal neoplastic polyps (i.e., adenomas)
    - Colorectal cancer
- Prior colectomy
- Lack of health insurance

C. Inclusion of Women and Minorities

The proposed study includes adults ages 45-49 receiving care within UCSDHS and those receiving care at UCSDHS, excluding only adults who are up to date with CRC screening, have prior diagnosis of inflammatory bowel disease (IBD), personal history of colorectal adenomas or CRC or who are uninsured. Given that our study does not exclude any women, includes both genders, and focuses on colorectal cancer screening uptake, we are confident there is no unacceptable inclusion or exclusion of women in our study.

The proposed study will include the recruitment of both minority and non-minority groups, all of whom are receiving care within UCSDHS. No racial or ethnic group are excluded from

participation in the study. Our goal is to assess colorectal cancer screening among adults ages 45-49, excluding only adults who had any prior colonoscopy, prior diagnosis of inflammatory bowel disease (IBD), personal history of colorectal adenomas or CRC or who are uninsured. To ensure representativeness of racial/ethnic groups experiencing colorectal cancer screening-related disparities, we oversampled Black or African American, Hispanic and Asian/Pacific Islander adults for our cohort.

D. Compensation for Participation in Interviews

Patient participants who complete an interview will be compensated with one $25 gift card within 2-4 weeks of participation. Provider participants who complete an interview will receive no compensation.

E. Rules for Ongoing Participation

Study participants are eligible to participate in other studies, including intervention studies, except for intervention studies pertaining to the colon or rectum.

Study Outcome Measurements

A. Primary Endpoints

Aim 1. Interview Measures

Interviews will focus on patient-level, provider-level and system-level constructs, which we view as interdependent, based on a prior CRC screening study by May et al. (**Figure 1**).[38] Patient factors will cover psychosocial and sociocultural factors, health literacy and behavior, perceived CRC risk and perceived screening benefits and harms. Provider factors will cover harms and benefits conferred by CRC screening and guideline knowledge and beliefs. System factors will cover access to care and new guideline implementation. Interviews will be semi-structured to offer flexibility to discuss topics of greatest interest to participants. Interviews will last approximately 45-60 minutes and be either in-person or video-based. If COVID-19-related conditions render in-person interviews unsafe, interviews will be conducted via a secure video-based meeting application (i.e., Microsoft Teams). Dr. Demb (PI) will be responsible for conducting the semi-structured interviews and will undergo training in conducting semi-structured interviews through enrollment in a qualitative research methods course at UCSD (Course: FPM 288). For non-English speakers, a translator will be accessed through electronic means such as the “Marti” platform used by UCSDHS for usual care translation.

We will notify participants prior to starting that the interviews will be recorded. Recording will be optional, such that the participant can opt out of recording at the time of informed consent. We will use a mobile recording device, which will be encrypted and physically kept in a secure location. Upon completion of interviews, the recordings will be transcribed and deleted from the recording device at the earliest opportunity. Transcriptions of the recordings will be coded to identify potential patterns and themes to compare with other participants. Transcriptions will also redact any directly identifying information.

Aim 2. Pilot Trial

The primary study endpoint is colorectal cancer (CRC) screening completion within 3 months of randomization. We plan to measure this using Healthcare Effectiveness Data and Information Set (HEDIS) documentation to inform our CRC screening uptake variable. This variable will incorporate CPT, Healthcare Common Procedural Coding System (HCPCS), and ICD-9/10 coding to identify FIT or guaiac fecal occult blood tests (CPT: 82270, 82274; HCPCS: G0328), flexible sigmoidoscopy (CPT: 45330-45335, 45337-45342, 45345-45347, 45349, 45350; HCPCS: G0104; ICD-9: 45.24), colonoscopy (*CPT/HCPCS codes mentioned in* ***Table 1***; ICD-9: 45.22, 45.23, 45.25, 45.42, 45.43), CT colonography (CPT: 74261-74263) and FIT-DNA (Cologuard) tests (CPT: 81528, HCPCS: G0464). We will also conduct manual EHR review to validate our HEDIS-defined algorithm. After the initial EHR query to define our study population, we will do manual EHR review two times during the follow-up period, once in the first month after study start to test the HEDIS-defined algorithm and a follow-up review in the second month after study start to validate the final algorithm. At the end of 3 months of study follow-up we will use the validated final algorithm to query for CRC screening completion.

B. Secondary Endpoints

Aim 2 Pilot Trial Secondary Outcomes

In the pilot trial, we will measure multiple outcomes to assess feasibility of a larger trial. We will measure the total number of participants who opt out of the pilot as a recruitment outcome. We will also measure the number of participants with undeliverable Cologuard or FIT kits, known as mail fail rate, as an intervention outcome. Among those with abnormal Cologuard or FIT, we will measure the proportion who are referred to colonoscopy and proportion who complete colonoscopy. We will measure the proportion who are referred to colonoscopy and the proportion who complete colonoscopy via manual EHR review of participants with abnormal Cologuard or

FIT results. We will conduct the manual EHR review 3 months, 6 months and 9 months after randomization, only among randomized study participants (those who provided signed HIPAA authorization and informed consent).

Other issues, such as challenges with identifying the correct assigned primary care provider, and challenges with logistics of outreach will be identified. Often in usual care, primary care providers who are contacted about a patient who is not assigned to them will respond to the contact by noting that the patient is not assigned to their care. If the study team receives such a response, we will manually review Epic encounter notes to see if there is documentation of a recent (within 1 year) primary care visit with a different provider. If an alternate provider is identified, this PCP will be contacted with the result. If an alternate provider is not identified, the study team will contact the study patient to see if they can identify a PCP who can be contacted by the study team. Also, prior to initiation of the study, we will contact the UCSD Health Wellness and Prevention Quality Committee to discuss input they may have on how the issue of incorrect assignment of PCPs is handled as part of usual care population health initiative. This discussion will be facilitated by Dr. Samir Gupta (co-I) who is a member of the Wellness and Prevention Quality Committee. The study team will work to identify solutions, including through informal consultation with primary providers and key points of contact involved with UC Health population health initiatives to identify practical solutions and update the protocol and submit relevant IRB modifications accordingly.

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Study Interventions

A. Primary Aim 2 Interventions

Mailed multi-target stool blood test (Cologuard) outreach.

The intervention to be tested in the pilot is mailed Cologuard outreach, a multi-component strategy that has been proven to be a highly acceptable test among current screening-eligible adults.[17,33] Cologuard is a USPSTF-recommended at-home screening test for blood in stool that additionally examines DNA markers in the stool to detect cancer. Its sensitivity to detect CRC is 92% and specificity is 86%.[37] Abnormal Cologuard results are followed up with a colonoscopy to identify and remove pre-cancerous polyps or diagnose early-stage CRC. Dr. Samir Gupta will be the ordering provider of the Cologuard tests for those participants randomized to the mailed Cologuard outreach. Participants randomized to mailed Cologuard outreach will receive:

1) advanced notification (primer) via mail one week prior to receiving the Cologuard test;

2) Cologuard test shipped directly to patient's home, with 2 months of personalized support to facilitate screening completion included. Included with the Cologuard test is a collection kit that may be returned at no cost to the patient via UPS (either by contact-free pick-up or drop-off at UPS). The Cologuard Customer Care Center also is available via phone or chat to aid with test completion.

3) Patient results will be sent to providers within 2 weeks of test completion and return.

Methods will be subject to change if pilot findings (Aim 2) or Aim 1 interview responses suggest alternative effective reminder strategies (e.g. text, robocalls). Patients with normal results will be sent a letter to repeat CRC screening in 3 years. Patients with abnormal results will be sent a letter encouraging follow up colonoscopy, and their primary care provider will be notified and requested to order colonoscopy. Patients with colonoscopy orders will receive usual care colonoscopy scheduling, preparation, and completion by the UCSDHS GI department.

Mailed fecal immunochemical test (FIT) outreach.

The intervention to be tested in the pilot is mailed FIT outreach, a multi-component strategy found to have the largest effect size to improve CRC screening uptake compared to usual care.[35,36] FIT is a USPSTF-recommended at-home screening test for blood in stool. Abnormal FIT results are followed up with a colonoscopy to identify and remove pre-cancerous polyps or diagnose early-stage CRC.[34] FIT test kits will be prepared at UCSD Health to be delivered to participants randomized to this study arm. Participants randomized to mailed FIT outreach will receive:

1) advanced notification (primer) via mail one week prior to receiving the FIT kit;

2) FIT kit with study information, invitation and instructions to complete FIT (adapted from Wang et al. study figure)[39] and how to opt-out; and

3) reminders via mail 14 days and 28 days after FIT kit receipt.

Methods will be subject to change if pilot findings (Aim 2) or Aim 1 interview responses suggest alternative effective reminder strategies (e.g. text, robocalls). Patients with normal results will be sent a letter to repeat CRC screening in a year. Patients with abnormal results will be sent a letter encouraging follow up colonoscopy, and their primary care provider will be notified and requested to order colonoscopy. Patients with colonoscopy orders will receive usual care colonoscopy scheduling, preparation, and completion by the UCSDHS GI department.

Human Rights Issues and Informed Consent

A. **Aim 1 Interviews**

Request for Waiver of Written Documented Informed Consent

Verbal informed consent will be obtained from all individuals—patient participants and provider participants—prior to participation in interviews. Informed consent requires that the potential participant understands the details of the study and agrees, without coercion, to participate in the study. In order to obtain informed consent, the following information shall be provided to each individual in the form of a document:

- The name of the study
- The name of the Principal Investigator
- An explanation that the study involves research
- An explanation that the purpose of the study is to identify an optimal CRC screening strategy that maximized CRC screening uptake.
- An explanation of the components of the study, including the interview.
- A description of the interview format and objectives.
- Patient participants only: An explanation that the patient's Medical Record Number will be used to identify records of medical care and to track the patient's CRC screening history.
- An explanation that all records will be kept confidential, but that records may be examined by representatives of UCSDHS.
- An explanation of whom to contact for answers to questions about the research and about research subjects' rights.
- A statement that participation in the study is voluntary and that a decision not to participate or to withdraw from the study after initially agreeing to participate will involve no penalty, loss of benefits or reduction in access to medical care.

- Patient participants only: A statement that there will be a one-time payment of a $25 gift card for participation in this study.

The use of a standardized consent document aids in assuring that participants receive adequate and consistent information about the interviews before consenting to participate. The study investigator will introduce and explain the study to the individual and present him or her with the detailed consent form and supplementary material to read and review. In some cases, this process may be initiated by telephone, such as for individuals who call the study investigator to learn more about the interviews. Telephone contact may only be initiated by the potential participant, unless they have previously been emailed an invitation to participate from the study team and been given the opportunity to opt out. Once the potential participant has been emailed an invitation letter, the study investigator will wait a minimum of one week for the potential participant to have the opportunity to opt out before initiating a phone call. Only after the participant has had the chance to review the consent document and ask any questions will they be asked to provide verbal consent to participate in the interview.

Considering the verbal consent method previously described, we request a waiver of written documented informed consent for our study. We request this waiver on the following grounds:

1) The proposed research does not meet the State of California's definition of a 'medical experiment'.
2) The proposed research presents no more than minimal risk of harm to the participants.
3) The proposed research involves no procedures for which written consent is normally required outside of the research context.
4) The potential participant will be presented with all the required elements of consent as previously described above.

The components of the interviews will be clearly described, as well as the general intent of the study. The potential participant will be informed that interview responses will be recorded by the study team. Trial participants recruited for interviews will be informed that their Medical

Record Number will be recorded in the research records as a unique identifier to link to their medical records. The individual will also be informed that any personal identifying information will be kept in a data-file separate from the files containing his or her other study data.

It must be ensured that the individual understands every aspect of the study, including its risks and benefits, prior to signing the informed consent. Our study population of adults ages 45-49 receiving care at UCSDHS with a documented primary care provider are likely to have a low prevalence of documented cognitive capacity issues. Indications of potentially diminished cognitive capacity include: 1) diagnosis of dementia or cognitive impairment, 2) presenting for an evaluation of dementia or cognitive impairment, 3) a report, in medical records that the subject has symptoms of dementia or cognitive impairment, 4) psychotic symptoms, bizarre or abnormal behavior exhibited by the individual and 5) an abnormal degree of confusion, forgetfulness, or difficulties in communication that is observed in the course of interacting with the individual. To ensure our study participants have adequate decision-making capacity to participate, we will initially review potential participants' electronic health records for documented conditions or circumstances that are associated with possible decrease in decision-making capacity. If at the time of consent or during the study period—participating in the interview—there is an indication that the participant's cognitive capacity is compromised, we will complete the University of California Office of the President Decision-Making Capacity Assessment Tool (hyperlink included) to measure the participant's cognitive capacity. If the participant is determined to lack decision-making capacity at this point, their responses will be excluded from the study.

The verbal consent of the individual to participate in the study will be recorded at the start of the interview.

B. Aim 2 Pilot Trial

Request for Partial Waiver of HIPAA Authorization for Pilot Trial Recruitment

For the Aim 2 pilot trial, we request a partial waiver of HIPAA authorization to identify eligible study participants to be recruited to the pilot trial.

Details and rationale for request of partial HIPAA authorization for recruitment of both intervention and control arms:

1. Source of PHI: electronic health record data
2. PHI to be accessed and recorded during recruitment: name, sex, age, race/ethnicity, colorectal cancer screening test documentation, prior history of colorectal cancer or inflammatory bowel disease, last primary care visit date, insurance status, prior colectomy date, dates of visit(s) to UCSD (not just primary care), mailing address, documented conditions or circumstances associated with decrease in decision-making capacity
3. Rationale for why PHI is essential for conduct of research: These data are required to determine study eligibility in a feasible and efficient matter.
4. Rationale for why requested PHI is minimal and necessary: These are the only data required to determine eligibility.
5. Rationale for why access, use, and disclosure of PHI presents no more than minimal risk: only research personnel will have access to the data, and data will only be used for recruitment purposes. Highly sensitive information is not required.
6. Plan for protecting identifiers: The list of eligible subjects will be kept either in electronic form with a password protected spreadsheet on a password protected server. Only UCSDHS staff and researchers associated with the project will have access to HIPAA-protected data until it is de-identified and share with the research team.
7. Plan for destruction of PHI: when the study is complete, PHI for all participants will be destroyed. This includes interview recordings and research records. Interview recordings will be deleted from the computer and the recording device. Electronic research records will be

erased. Any paper-based research records will be securely shredded and disposed of in secure waste receptacles.

8. Rationale for waiver: The waiver involves minimal risk, does not compromise patient rights or welfare, and allows the research to be feasibly done.

Individuals eligible for pilot trial:

HIPAA Authorization and Informed consent will be obtained electronically via eConsent forms within REDCap from all eligible individuals prior to randomization to trial intervention or control group. HIPAA authorization enables the research team to provide relevant patient information to Exact Sciences, the company mailing and implementing the Cologuard test, and follow eligible individuals randomized to the intervention or control arm for outcome measurement via the individual's electronic health record. Informed consent requires that the potential participant understands the details of the study and agrees, without coercion, to participation in the study. To obtain informed consent, the following information shall be provided to each individual:

- The name of the study
- The name of the Principal Investigator
- An explanation that the study involves research.
- An explanation that the purpose of the study is to identify an optimal CRC screening strategy that maximized CRC screening uptake.
- An explanation of the components of the study, including the two study arms to which a participant might be randomized.
- An explanation that the patient's Medical Record Number will be used to identify records of medical care and to track the patient's CRC screening history.

- An explanation that patients randomized to mailed Cologuard outreach will have test orders that include their name, medical record number, date of birth, sex, address, phone number, and health insurance information provided to Exact Sciences who will mail and process the Cologuard test, and that those randomized to mailed FIT will have their name, address, and phone number used for purposes of mailed FIT outreach.
- An explanation that costs of the tests within study arms will be covered by the patient's health insurance as an essential health benefit covered under the Affordable Care Act.
- An explanation that all records will be kept confidential, but that records may be examined by representatives of UCSDHS.
- An explanation of whom to contact for answers to questions about the research and about research subjects' rights.
- A statement that participation in the study is voluntary and that a decision not to participate or to withdraw from the study after initially agreeing to participate will involve no penalty, loss of benefits or reduction in access to medical care.

Merely obtaining a signed consent document does not constitute informed consent. However, the use of a standardized consent form aids in assuring that participants receive adequate and consistent information about the pilot trial and have consented to participate. The study investigator will provide written documentation that explains the study to the individual and present him or her with the detailed consent form to read and review. In some cases, this process may be initiated by telephone, such as for individuals who call the study investigator to learn more about the pilot trial. Telephone contact may only be initiated by the potential participant. While we will strongly encourage a face-to-face informed consent process, such a process for this type of study is not ideal, because it will less closely reflect the future state we are trying to mimic, in which the convenience of mail-based outreach can be used to facilitate participation in CRC screening. Thus, we propose a process whereby the informed consent

form and HIPAA Authorization form are provided via 1) an electronic eConsent form within REDCap. A postcard will be mailed to the potential participant's home, including a QR code where the potential participant may access, review, and sign the informed consent and HIPAA Authorization forms.

The components of the pilot trial will be clearly described, including the potential interventions participants could be exposed to, as well as the general intent of the study. The potential participant will be notified that randomization to the Cologuard intervention would lead to their name, medical record number, date of birth, sex, address, phone number, and health insurance information being shared with Exact Sciences to facilitate mailing of the Cologuard test and delivery of test results.

It must be ensured that the individual understands every aspect of the study, including its risks and benefits, prior to signing the informed consent. Our study population of adults ages 45-49 receiving care at UCSDHS with a documented primary care provider are likely to have a low prevalence of documented cognitive capacity issues. Indications of potentially diminished cognitive capacity include: 1) diagnosis of dementia or cognitive impairment, 2) presenting for an evaluation of dementia or cognitive impairment, 3) a report, in medical records that the subject has symptoms of dementia or cognitive impairment, 4) psychotic symptoms, bizarre or abnormal behavior exhibited by the individual and 5) an abnormal degree of confusion, forgetfulness, or difficulties in communication that is observed in the course of interacting with the individual. To ensure our study participants have adequate decision-making capacity to participate, we will initially review potential participants' electronic health records for documented conditions or circumstances that are associated with possible decrease in decision-making capacity. If at the time of consent or during the study period of the pilot trial there is an indication that the participant's cognitive capacity is compromised, we will complete the University of California Office of the President Decision-Making Capacity Assessment Tool (hyperlink included) to measure the participant's cognitive capacity. If the participant is

determined to lack decision-making capacity at this point, their follow-up will be excluded from the study.

The consent of the individual to participate in the study and HIPAA research authorization will be recorded electronically on an eConsent form within REDCap. Copies of the signed and dated consent and HIPAA research authorization forms will be provided to the participant and placed in the participant's study file.

C. Risk and Benefits

Risks

Research risks include the following:

i. Loss of confidentiality or privacy due to disclosure of research data, including protected health information. Loss of confidentiality or privacy could lead to physical, psychological, social, legal, or financial harms due to the personal nature of the data used. The seriousness of loss of privacy or confidentiality would be substantial. However, the likelihood of loss of confidentiality or privacy, and subsequent harms, is low due to the study procedures we have planned to protect research data. For example, only study-related personnel will have access to protected health data which will be saved either electronically on a password protected HIPAA-secured server with access to the study related folder only granted to study personnel, or in locked filing cabinets in a locked office onsite at UCSDHS with limited access. Additionally, Exact Sciences provides over 3 million tests annually across the nation as part of usual care CRC screening, and are subject to federal and state regulations for protection of healthcare related PHI.

ii. The interventions for promoting CRC screening pose minimal risk for physical or mental harm. There is a risk of loss of confidentiality that will be minimized by collecting minimal data required for research, only providing the minimum necessary information to Exact Sciences to facilitate mailing and test implementation in the case of the mailed Cologuard

outreach trial arm and keeping the data secure. Adverse physical effects are expected to be minimal because CRC screening with FIT or Cologuard are noninvasive tests, recommended as standard of care. If needed, all participants will have access to medical and mental health services by virtue of the services available to all registered patients. By having the primary care physician aware of participant involvement, we should be able to minimize many risks to the participant. Individuals may feel some discomfort by addressing issues such as cancer. Nevertheless, UCSDHS has a strong behavioral health department and regular referral systems are in place.

iii. The interventions for promoting CRC screening are covered as essential health benefits for insured individuals ages 45-75 at average risk for colorectal cancer, based on the Affordable Care Act. While this coverage is intended to protect patients from paying out-of-pocket costs for CRC screening, there are very rare cases where patients might be responsible for paying a portion of the test cost not covered by their insurance plan. We anticipate this will impact very few, if any participants in our study.

Benefits

There are not guaranteed benefits for participants whose data is used in the study. However, the following are potential benefits to participants:

1. Interview participants may learn about CRC screening and contribute to improved patient care in the future.
2. Participants in the mailed FIT intervention and Cologuard intervention may benefit from completing CRC screening, which can increase chances of detecting CRC early and even preventing CRC development.
3. Future patients may benefit from knowledge gained that informs interventions for improving CRC screening participation.

The main risks of the study are loss of confidentiality and privacy (which will be minimized through our data protection procedures). For the participants, the main benefits are potential to detect early-stage CRC, and gain knowledge that may improve cancer prevention for participants. Thus, considering potential for this research to advance CRC prevention, the benefits outweigh potential risks.

D. Protection Against Risk

Planned procedures for protecting against/minimizing potential risks

Protection of privacy and data security. This will be accomplished by the following steps:

- Limiting access to research data to study personnel
- Storing all electronic data on a password protected research drive within a secure HIPAA research server
- Storing all paper records in a locked filing cabinet within a locked office
- Only sharing coded data for analysis purposes with UCSD
- IRB required training for research personnel will be kept current for all study personnel
- Names will not be recorded or kept in analytic datasets
- Only de-identified and aggregated data will be used for study presentations and publications

Protection of patient participants of receiving unanticipated costs from insurance

To ensure potential participants are eligible for our pilot trial, we will assess patient participant eligibility criteria at the point of recruitment to ensure that they qualify for colorectal cancer screening. This will limit the likelihood of incurring costs by ensuring the patient is age-eligible, does not have any of the excluding risk factors, and has not received prior screening or diagnostic testing that precludes them from receiving one of the screening tests in our study.

Protection of provider participants from intimidation or coercion to participate.

We are particularly interested in the perspectives of providers actively involved in referral to and coordination of colorectal cancer screening at UCSDHS. These providers will offer important information on barriers and facilitators of colorectal cancer screening among adults ages 45-49, who are newly eligible based on updated screening guidelines. The provider perspective offers additional context to better understand the various factors ultimately impacting screening uptake. Providers will be directly recruited to participate and will have autonomy to choose whether they wish to participate. They will not be coerced or intimidated into participation. Measures to prevent coercion will include not allowing a provider's supervisor to know who elected to participate or not (anonymizing the provider if they agree to participate) and assuring providers that deciding to participate will not have a negative effect on that provider's job or standing at work. Provider participant responses to interviews will be anonymized, such that they cannot be traced back to a specific provider participant. When presenting research findings, all provider participants will be referred to as “providers” when discussing their responses, such that there is no way to trace back individual responses to an individual provider or someone within a specific discipline.

Interview participants will be provided the number for the UCSD Office of IRB Administration (OIA), as well as the PI, and may express any concerns. The fact sheet and the recruiting scripts will clearly inform interview participants that participation is voluntary and will not affect their employment in any way. If the study team becomes aware of any unanticipated adverse events, the Office of IRB Administration (OIA) will be informed promptly, and a plan to address the adverse event will be proposed. Responsibility for supervising implementation of the plan lies with the PIs.

We have adequate resources to support our risk management procedures, including the support of the primary mentor. Dr. Gupta is a licensed physician and practicing Gastroenterologist. He will provide medical oversight to the study. The study will follow the standard internal referral mechanisms set forth in the UCSDHS clinics. UCSDHS provides a

comprehensive spectrum of primary care services. In addition, UCSDHS has a standard referral system for abnormal cancer screenings. Any participant who becomes uninsured and in need of services will be referred to the appropriate cancer diagnostic and treatment resources, as is the case with all UCSDHS patients. UCSD study staff will work to ensure patients get connected with any indicated services.

Likely effectiveness of planned procedures for protecting against/minimizing risks

We anticipate that the steps outlined above will be highly effective for minimizing risk. Intervention in event of adverse effects to the subjects: In the event of concern for loss of confidentiality and/or disclosure of research related data to unauthorized personnel, we will take the following steps:

- The PI and research team will review the event immediately, and within 1 business day inform the UCSD Human Subjects (IRB) Subcommittee.

In the event of any adverse event, we will work with the UCSD Human Subjects (IRB) Subcommittee to plan corrective action, and also initiate actions to prevent further research related risks.

Stratification and Randomization

A. Randomization

For the Aim 2 Pilot Trial, we will use the UCSDHS EHR and conduct a query for a list of all potential participants who meet the eligibility criteria. We will use both Epic and Care Everywhere platforms to ascertain eligibility criteria for recruitment. Among the list of adults deemed eligible for recruitment, we will stratify individuals based on their EHR-documented race/ethnicity into one of five groups: Non-Hispanic White, Black, Hispanic, Asian/Pacific Islander, Other. From these groups, we will select a list of 20 individuals to be recruited. In sum, the 100 individuals will be comprised of 20 individuals selected at random from 5 self-reported racial/ethnic groups, with the intent that each racial/ethnic group will have 10 individuals represented in the mailed Cologuard outreach and mailed FIT outreach (each group makes up 20% of the sample in each arm). This will ensure equal balance of participants from each racial/ethnic group in each trial arm.

Eligible individuals will be mailed a postcard briefly describing the study and asking patients to scan a QR code if they are interested in participating. The QR code will take eligible individuals to an eConsent page within REDCap where they will be provided with informed consent and HIPAA Authorization forms that will need to be completed to participate in the study. Electronically completed and signed informed consent and HIPAA authorization forms will be required prior to randomization. HIPAA Authorization is necessary to release relevant patient information to Exact Sciences, the company that will mail and implement the Cologuard test, should the participant be randomized to that group. Additionally, HIPAA Authorization ensures participant electronic health records may be examined to measure the study's outcomes of interest over the course of study follow-up.

If individuals decline participation or do not sign HIPAA authorization and informed consent documents, they will be replaced by an individual from the stratified race/ethnicity group. Recruitment will continue until a sample size of 50 individuals per trial arm (mailed FIT

intervention and usual care) who consent to participation in the study is achieved. Each group will be followed for 6 months for the primary outcome: completion of any CRC screening test (FIT, FIT-DNA [Cologuard], sigmoidoscopy, colonoscopy, or CT Colonography), measured by evidence of screening documented within the EHR using Healthcare Effectiveness Data and Information Set (HEDIS) criteria.

B. Blinding

Due to the nature of the interventions, the study team will not be blinded to group assignment. Patients will be notified prior to randomization of the existence of two study arms (mailed Cologuard outreach and mailed FIT outreach), and once randomized, will know whether they were assigned to Cologuard or mailed FIT outreach. From the date of randomization, participants will be followed for 3 months to ascertain the primary outcome: CRC screening completion, measured by evidence of screening documented within the EHR. Additional passive follow up through manual chart review will continue 9 months post randomization.

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