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Formative work to understand and improve colorectal cancer screening in Mexico and the United States

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Formative work to understand and improve colorectal cancer screening in Mexico and the United States

by
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DISSERTATION
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of the
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DEDICATION AND ACKNOWLEDGEMENTS

A mi mamá, Anita y Carlos. Sin todo su apoyo y amor esto no hubiera sido posible. A Mamá Anita, quien me enseñó que con perseverancia se puede cumplir cualquier sueño. A mis hermanos, papá, tíos, tías, primos, primas, abuelo, abuela, amigas y amigos. To my younger self and to all Mexican women, especially the ones who came before me, for their relentless perseverance.

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CONTRIBUTIONS

Dr. Martin Lajous contributed to the design and implementation of our feasibility studies conducted in Mexico City and Nuevo León (Chapters 1 and 2).

Dr. Karla Unger Saldaña and Dr. Minerva Saldaña Téllez guided all interviews and focus groups, analyzed all transcripts, and contributed to the design of our feasibility study conducted in Mexico City (Chapter 1).

Formative work to understand and improve colorectal cancer screening in Mexico and the United States

Priscilla Espinosa Tamez

ABSTRACT

Colorectal cancer (CRC) remains a significant public health problem worldwide, with incidence and mortality increasing, especially in low- and middle-income countries. Effective screening programs are crucial for early detection and to reduce the burden of this disease. In Mexico, where there is currently no national CRC screening program in place, CRC mortality has increased significantly over the last two decades. In contrast, in the United States (US) and specifically in California, the state with the highest number of Hispanic and Latino populations in the US, CRC screening has been available for decades, and a decline in incidence and mortality has been observed in the past four decades.

Considering these trends and stages in the implementation of colorectal cancer screening programs in both contexts, the objective of this dissertation was to conduct formative work to understand and improve colorectal cancer screening in both contexts. In Mexico, this dissertation focuses on studying the feasibility of integrating fecal immunochemical test-based screening into an existing door-to-door vaccination program in Mexico City (Chapter 1), and in an integrated healthcare system in Nuevo Leon (Chapter 2). In the US, specifically in California, it focuses on assessing the ecological association between CRC screening and late-stage disease at diagnosis and identifying zones where efforts to increase screening and to understand and address barriers are needed to improve CRC outcomes (Chapter 3).

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LIST OF ABBREVIATIONS

AAPI	Asian American and Pacific Islander
BBPS	Boston Bowel Preparation Scale
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CFIR	Consolidated Framework for Implementation Research
CI	Confidence interval
CRC	Colorectal cancer
DREAM	Disparities Research: Environment And oMics
EHR	Electronic health record
FIT	fecal immunochemical test
FOBT	Fecal occult blood test
FRAME	Framework for Reporting Adaptations and Modifications-Expanded
gFOBT	Guaiac-based fecal occult blood test
HBM	Health Belief Model
HG	Hemoglobin
IARC	International Agency for Research on Cancer
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ICE	Index of concentration at the extremes
IMSS	Instituto Mexicano del Seguro Social
INCan	Instituto Nacional de Cancerologia
INSABI	Instituto de Salud para el Bienestar

INSP	Instituto Nacional de Salud Publica
IRB	Institutional Review Boards
ISSSTE	Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado
ISSSTELEON	Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado de Nuevo Leon
LEP	Limited English proficiency
LMICs	lower- and middle-income countries
MSAs	Minimal sufficient adjustment set
NG	Nanogram
PPV	Positive predictive value
RA	Recruitment appointment
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
SES	Socioeconomic status
UCSF	University of California San Francisco
US	United States of America

CHAPTER 1. FEASIBILITY OF PROVIDING COLORECTAL CANCER SCREENING IN THE CONTEXT OF DOOR-TO-DOOR VACCINATION ACTIVITIES IN MEXICO CITY

Introduction

Colorectal cancer (CRC) is a preventable and curable disease with early diagnosis and screening.[1] Yet, globally, CRC remains one of the most frequent causes of cancer mortality.[2,3] In 2022, CRC claimed 900,000 lives, with most of these deaths occurring in lower- and middle-income countries (LMICs).[2,3] In Mexico, CRC is the leading cause of cancer mortality (5.5 deaths per 100,000)[3] and the burden of disease is rapidly increasing.[4,5] Urban communities are particularly affected likely because of marked epidemiological and nutritional transitions, including higher meat, animal products, and refined carbohydrate intake.[6–9] In Mexico City, the CRC mortality rate nearly tripled between 1990 and 2021, to 12.1 deaths per 100,000.[10]

In Mexico, CRC is often diagnosed at an advanced disease stage, with only half of patients surviving the disease 5 years after diagnosis.[11] The International Agency for Research on Cancer (IARC) recommends a biennial fecal immunochemical test (FIT) for adults aged 50 to 75, followed by diagnostic colonoscopy and subsequent treatment, if indicated, as a cost-effective approach to reduce CRC mortality.[12] There are currently no population-based CRC screening programs in Mexico.[11,13] Furthermore, there are multiple steps along the CRC screening process where significant barriers threaten the completion of the diagnostic work-up and treatment initiation particularly in low-resource settings.[14,15] Screening programs that address barriers at multiple levels and steps in the screening process have been shown to be more effective and sustainable than programs that target only one part of the health system or screening process.[16,17]

Population health programs administered by publicly operated health clinics in Mexico City provide a unique opportunity for CRC screening, with existing door-to-door neighborhood outreach programs serving as a potential setting for education about CRC and the distribution and collection of FIT kits for average-risk adults. In this study, we aimed to develop and pilot test the implementation of CRC screening activities in the context of an existing door-to-door vaccination program in Mexico City.

Methods

Study population and program setting

Following IARC's recommendation, our target population was average-risk adults (i.e., no personal or family history of CRC in first-degree relatives, no active rectal bleeding) aged 50 to 75 years. In collaboration with Mexico City's Health Department, we selected the Miguel Hidalgo district. The district was chosen because a large proportion of residents in this area were aged 50 or older and because the primary care clinic that serves this district had well-performing door-to-door vaccination programs in place. The clinic also had adequate facilities for the program (e.g., refrigerated storage for FIT kits), provided daily clinical service to the community every day of the week, and was located close to the general hospital where participants with abnormal FIT could be sent for colonoscopy.

We developed the program in two stages. First, we interviewed potential end-users of the program, created educational materials, and co-designed the screening program in collaboration with local experts. Second, we implemented and evaluated the program, with adaptations as necessary due to the COVID-19 pandemic.

Program Design

Exploratory formative research. We conducted 31 semi-structured interviews with Mexico City's Health Department staff members (n=17), primary care personnel from the clinic (n=10), and key personnel from the colonoscopy unit at the referral hospital (n=4). In the interviews, we assessed CRC screening awareness, perceived barriers and facilitators to implementation of a CRC screening program in this setting, discussed the existing door-to-door programs offered at the clinic, existing procedures to diagnose and refer patients in whom CRC was suspected, and ideas to facilitate implementation of CRC screening. We also conducted three focus groups (total n=26) with adults from the study population. Focus group participants were recruited through posters placed in the community and through study personnel outreach to the health clinic, a public recreation center, and a neighborhood church, and continued until data saturation was reached. Qualitative research participants were offered a bag of groceries as compensation for their time and shared knowledge. We assessed CRC awareness, attitudes, beliefs, and perceived barriers and facilitators to CRC screening, as well as attitudes toward vaccination programs, the local primary clinic, and the local hospital. After informed consent, interviews were led by two qualitative researchers, recorded, de-identified, transcribed, and analyzed with Atlas.ti software.[18] We employed the Constant Comparison method, a core technique of grounded theory, for the analysis, organizing themes to align with the Health Belief Model (HBM)[19,20] and Consolidated Framework for Implementation Research (CFIR).[21]

Educational materials design. Based on the results of our interviews and focus groups, we collaborated with health education professionals from Mexico's Instituto Nacional de Salud Publica (INSP) to create two postcards, a video, a brochure, and a poster for patient education. We conducted four focus groups with community members (total n=40), following the same

recruitment strategy as with our initial formative research, to pretest the educational materials and assess their acceptability, clarity, cultural appropriateness, and motivational effect. We adjusted the design and contents of the materials based on the results of these focus groups (e.g. change of images, reduction of text, rewording of the hook phrase). We then conducted two final focus groups (n=26) to reassess the impact of the changes on acceptability, clarity, cultural appropriateness, and motivational effect. The final materials were found to be acceptable, clear, appropriate, and motivational. (**Supplemental Table S1.3**)

Screening program co-design. Next, we designed the program in collaboration with decision-makers from the primary care clinic and colonoscopy referral site. Outreach activities were reviewed and refined. For example, personnel that would recruit participants would be hired by the study, join the clinic's regular vaccination activities, and offer CRC screening after vaccination was offered in each household. We were also able to simplify the referral process for those who would need a colonoscopy after FIT, reducing the number of required visits prior to a colonoscopy from five to two.

Program implementation

CRC screening outreach and participant recruitment. We promoted our program using posters that were placed around the clinic, at a local market, and at a local public recreation center. We hired three experienced health promoters (personnel who conduct community outreach to provide education on public health topics) for participant recruitment. Health promoters would accompany primary care clinic personnel during their regular vaccination door-to-door home visits (8 am – 2 pm).

In homes where a resident in the target age group was not present during the visit, a short explanation would be given to a relative along with a postcard that could be exchanged for a FIT

kit at the clinic. In homes where potential participants were present, health promoters would assess if inclusion criteria were met, explain the program with the support of the video and brochure, and obtain written informed consent. Health promoters tracked how many homes were visited, eligible population contacted, and population that declined. High-risk participants identified during recruitment were informed that they should schedule a primary care appointment at the clinic to be referred to the Gastroenterology department and colonoscopy accordingly.

Participants who agreed to participate in the study would receive a FIT kit (OC FIT-CHEK, Polymedco, quantitative test) with instructions to keep the kit in their refrigerator after sample collection and return it to the clinic within a week. Study personnel would collect participant information at enrollment, including age, sex, educational attainment (highest level of education completed), health insurance provider, self-reported height, weight, diagnosis of diabetes, and tobacco smoking (never, past or current). Participants who did not return the FIT within one week would receive a reminder phone call. FIT kits would be stored in a refrigerator at the clinic until they could be transported for processing following the manufacturer's guidelines. Participant recruitment began on February 20, 2020, but was suspended on March 20, 2020, due to the COVID-19 pandemic.

Screening follow-up. Participants were originally to be scheduled to receive their results at the clinic. Those with an abnormal FIT result (≥20 nanograms (ng) of hemoglobin (Hg)/mL) would be referred for colonoscopy at the nearby hospital. Because of safety concerns related to the onset of the COVID-19 pandemic, procedures for FIT follow-up had to be modified in several ways. FIT results could not be conveyed in person at the clinic and instead were delivered by phone or video call. Because the local endoscopy unit had to be shut down, participants with abnormal FIT results had to be referred for colonoscopy at the endoscopy unit in Mexico's Instituto Nacional

de Cancerologia (INCan), 90 minutes away by public transportation. Participants referred to colonoscopy were provided with personal protective equipment and free private transportation to INCan. Prior to colonoscopy, we delivered polyethylene glycol 3350 (Nulytely) for bowel preparation to participants' homes. At INCan, a rapid blood coagulation test was performed before the procedure. Colonoscopy findings were explained to participants by INCan staff at discharge, and pathology results were provided and explained at a follow-up appointment at INCan. Participants received follow-up recommendations according to National Comprehensive Cancer Network guidelines.[22] We recorded colonoscopy quality indicators, including Boston Bowel Preparation Scale (BBPS)[23], withdrawal time, and number of patients with adenoma.[24] High-risk pre-cancerous findings were defined as having 3 or more adenomas, a tubular adenoma of 10mm or more, or an adenoma with villous histology or high-grade dysplasia.[25] Positive predictive value (PPV) for high-risk adenoma was calculated as the proportion of participants who had high-risk adenoma findings after colonoscopy, among participants with an abnormal FIT result. PPV confidence interval was estimated using the Clopper–Pearson method.[26]

Screening program evaluation. We used the RE-AIM (reach, effectiveness, adoption, implementation, and maintenance) framework to evaluate our intervention.[27,28] Due to the COVID-19 pandemic restrictions, we were unable to observe the extent of program adoption over time or to evaluate the potential for program maintenance. Thus, we focused on program reach, effectiveness, and implementation. For reach, we collected data on the number of houses visited and residents contacted. For effectiveness, we determined FIT return and colonoscopy completion. For implementation, we recorded observations of study personnel and documented adaptations that were made during the study to accommodate the needs of patients and healthcare personnel both during the initial roll-out phase of the program and in response to changing public

health conditions. After the intervention was completed, we also assessed the acceptability, appropriateness, and feasibility of the program for health promoters, nurses, and doctors who participated, inviting them to provide feedback through an anonymous voluntary online self-administered survey developed by Weiner et al.[29,30] Each of the measures (acceptability, appropriateness, and feasibility) is composed of 4 items each, with 5-point Likert scale responses. A final average value for each was obtained, ranging between 1 and 5, where higher scores indicate greater acceptability, appropriateness, or feasibility.[30] Finally, we assessed the acceptability of the program from the perspective of patient participants in the study using a self-administered questionnaire of our own design. Participants answered the anonymous voluntary survey on a tablet available after they delivered their FIT kit to the clinic, and for those who completed their colonoscopy, an additional online survey was administered via email or text.

All guides, materials, procedures, and informed consent forms were reviewed and approved by INSP's and Mexico City's Health Department Institutional Review Boards (IRB). This study was exempt from (University of California San Francisco) UCSF's IRB approval.

Results

Program Design

Barriers to CRC screening with FIT in this community (**Figure 1.1**) included the complexity of screening, lack of knowledge about CRC screening among both patients and health personnel, perception of multiple barriers to screening (fear of cancer, fear of colonoscopy, embarrassment), and characteristics of the neighborhood primary care clinic and the local hospital (understaffed, lack of supplies and work overload). The main facilitators identified included the perception that the FIT was easy to do and could be completed at home and the perception of a good working environment and strong leadership at the clinic and hospital. Evaluation of the modified versions

of educational materials revealed that they were perceived as attractive, simple, highly understandable, culturally appropriate, and would motivate people to complete a FIT. (**Supplemental Table S1.3**)

Program implementation

For reach, we found that the health promoters visited 412 homes, identified 218 people within the recommended age range for CRC screening, and distributed educational materials to all who were eligible. (**Figure 1.2**) Promoters found 155/218 people who met eligibility criteria during their visit and invited them to the study using the educational booklet and video developed for the program. Among those, 80.6% (125/155) accepted participation and were given a FIT kit in their home. There were 23/218 additional individuals deemed potentially eligible for participation who were not at home during the promoters' visits, for which a postcard that could be exchanged for a FIT kit at the clinic was delivered. Seven of these individuals exchanged the postcard for a FIT kit. Thus, a total of 132 participants were successfully recruited and provided with a FIT kit between February 20 and March 20, 2020. Participants' sociodemographic characteristics and risk factors for CRC are shown in **Table 1.1.** The mean age of participants was 62.0 (±6.8) years, and most were women (63.6%). Most of the participants (66.7%) had an educational level of less than high school and had some type of health insurance (87.9%). Additionally, 31.8% self-reported having diabetes mellitus, and 21.2% were self-reported current smokers, conditions known to increase the risk of CRC.

In terms of the effectiveness of the intervention, we found that 71.2% (n=94) of the 132 successfully recruited program participants returned their FIT to the primary care clinic. The mean kit return time was 4.7 days. 21.3% (20/94) of the participants had an abnormal FIT result and were referred to colonoscopy (**Figure 1.2**). 50% (10/20) completed colonoscopy. Of the 10

participants who did not complete colonoscopy, two were lost to follow-up, two had their colonoscopy deferred due to medical risks of the procedure, one had an incomplete colonoscopy (stenosis), and five declined the procedure when offered. The latter five reported that they declined due to fear of visiting a hospital at the height of the COVID-19 pandemic, even if they were using protective equipment and had free individual transportation. All 10 successful colonoscopies performed had an adequate BBPS[23] score ≥6, and a colonoscope withdrawal time ≥6 minutes. No cancers were found, but at least one adenoma was found in 50% (5) of the procedures. PPV for high-risk lesions was 20% (95% CI: 2.5-55.6%). Colonoscopy findings for these participants are shown in **Table 1.2**.

During the first month of study implementation, participant recruitment proceeded successfully and at a relatively rapid rate. However, several adaptations were made even before the onset of the COVID-19 pandemic. For example, the vaccination program had been designed for households with children, and it was originally assumed that these households would also include older individuals who would be eligible for CRC screening. However, many households with children did not include such individuals, whereas they were present in other neighboring homes. Thus, the outreach was expanded to include households in the neighborhood even if there were no children present and in need of vaccination. We also modified FIT return hours to include weekends to maximize convenience for study participants. However, only two FIT kits were returned during the weekend. Program adaptations in response to COVID-19 pandemic restrictions were described above.

For our Acceptability, Appropriateness, and Feasibility evaluation survey for healthcare providers, we received responses from 39 health promoters, nurses, and physicians who participated in the program. Scores for the domains show that, on average, healthcare providers

strongly agree with the Acceptability (mean=4.0/5.0), Appropriateness (mean=4.0/5.0), and Feasibility (mean=3.9/5.0) of the intervention. More than 80% (110/132) of program participants responded to our post-FIT evaluation survey and 9/10 to our post-colonoscopy survey. Overall, respondents fully agreed that our approach for FIT distribution and return was acceptable (110/110). Our colonoscopy process was moderately acceptable: 7 out of 9 participants who received a colonoscopy and responded to the survey agreed it was an acceptable strategy, while one neither agreed nor disagreed, and one strongly disagreed. All respondents considered that the steps they had to follow during FIT completion and return and colonoscopy were easy to understand. We observed that 21% (23/110) neither agreed nor disagreed on whether many people in their community would find our approach to CRC screening appropriate, while the rest agreed they would find it appropriate.

Discussion

Our experience developing and implementing a population-based screening program in the context of a neighborhood vaccination program yielded encouraging results related to the potential feasibility and acceptability of population-based CRC screening in Mexico City. Despite the COVID-19 pandemic, we observed that health workers were able to proficiently understand and apply the fundamentals of CRC screening and use tailored patient education materials to offer FIT and facilitate follow-up with colonoscopy, even in the context of a looming global pandemic.

Among those who were provided with FIT kits, test completion was 71%. Of those with abnormal test results, half were navigated to colonoscopy, even with patient fear about going near hospitals in the midst of the pandemic. These completion rates, achieved under challenging

circumstances, compare well with benchmarks for screening participation set by others: 60% FIT uptake and 80% colonoscopy completion after abnormal FIT.[31,32]

Participation in CRC screening varies widely across regions and countries. Return of stool blood test screening for CRC was documented at 16.1% in Canada, 21% in South Korea, and 48% in the United States (US). Colonoscopy completion was observed at 31% in South Korea, 76% in the USA, and 81% in Canada.[32–36] During the early part of the COVID-19 pandemic, a 28% to 100% decline in colorectal cancer screening was documented across countries.[37] Referrals to colonoscopies decreased by 43%, completion of colonoscopies decreased by 66%, and surveillance colonoscopies decreased 45-79%.[37]

In Mexico, previous studies obtained higher results than what we observed: 88% of participants returned their FIT kit in Veracruz[38], and 91% in Mexico City.[39] Similarly, these studies observed higher colonoscopy completion: 88% in Veracruz[38] and 78% in Mexico City.[39] However, these studies were conducted in highly controlled conditions with intense follow-up contact for FIT return and colonoscopy completion and recruiting from a highly educated and motivated group of INCan workers and family members, respectively. In our door-to-door CRC screening study, participants reported that the main reason for not accepting colonoscopy was fear of getting COVID-19, concerns that hopefully no longer persist. As in most organized CRC screening programs, we identified opportunities for improvement at each step of the screening process: providing FIT to those who are eligible, navigating patients to complete FIT when offered, and navigating patients through the process of colonoscopy. We observed that most of the recruited participants were women (64%), which represented the demographic characteristics of the population present at home during vaccination activities. This challenge in our approach may require the development of tailored outreach strategies for male populations. That said, among

screening program participants, most reported that they found this strategy acceptable and that their peers would find it appropriate. Therefore, we believe our results provide evidence of the population's and healthcare personnel's willingness to participate in CRC screening when offered in the context of door-to-door population outreach in Mexico, if and when resources become available to support these activities on a larger scale.

Additionally, we found that FIT-based CRC screening using ≥20ngHg/ml as a cut-point for deeming a test result to be "abnormal" resulted in a high rate of referral for colonoscopy (21%) compared to referral rates observed in screening programs that have been implemented in higher-income countries.[40–42] This is likely driven by the combination of our never-screened target population and our use of a lower cutoff point (20 vs 100ng Hg/ml in other countries). FIT positivity with a cutoff ≥100ng of Hg/mL has been documented as 2% in England[32], 5% in the USA[32,43], 7% in Croatia[32], 11% in Uruguay[44], 10% in Brazil[45], and 9%[46] in Thailand, while FIT positivity with a cutoff ≥20ngHg/ml in a previous study in Mexico City was 15%. Additionally, the positive predictive value for high-risk adenomas in our study (20%) was comparable to what has been observed in France (20%)[47], the Czech Republic (17%)[41], and Mexico City (20%)[39]. Nevertheless, considering these results in the context of a middle-income country such as Mexico, where endoscopy capacity is growing but still limited, adopting a higher FIT result threshold for colonoscopy referral might be most practical.

Finally, from an implementation perspective, we gained experience in the implementation of a community-based screening program and the development of educational materials and standard operating procedures that can be harnessed for future CRC screening projects in Mexico. Moreover, we established a strong implementation research team and partnerships between

researchers, clinicians, healthcare facilities, and health authorities that will allow for future community-based CRC screening-related projects.

Strengths of our study include the use of mixed methods, which included community engagement to develop educational materials and staff for intervention design, followed by assessment of the intervention's effectiveness. Furthermore, this is the first study of population-based screening in the context of a door-to-door vaccination campaign in Mexico. Evidence from community-based programs like this will be crucial for the development of equitable screening strategies for a healthcare system that currently aims to transition into being comprehensive, integrated, and universal.[48,49] Limitations of our study include small sample size, interruption of study recruitment due to COVID-19, the effects of fear of getting COVID-19 during participation, and that recruitment activities were performed by health promoters hired by the project and not clinic personnel.

Conclusion

Our study allowed us to design and test a novel population-based CRC screening strategy in Mexico City. FIT was well-accepted when offered at people's homes in the context of an established, well-organized door-to-door vaccination program. If promoters are able to offer it during regular activities, and barriers to colonoscopy can be addressed, this program shows significant potential for implementation. Our results and materials are also relevant scientific contributions to support CRC screening in Mexico and other middle-income countries that seek to implement population-based CRC screening programs. Further research is needed regarding the feasibility and effectiveness of 1) scaling up population-based CRC screening programs through door-to-door outreach in Mexico, 2) clinic-based CRC screening strategies in other settings in Mexico, especially in integrated health systems with resources to provide colonoscopy

and cancer treatment, and 3) other evidence-based interventions and implementation strategies that would effectively support CRC screening, diagnosis, and treatment in Mexico.

Funding

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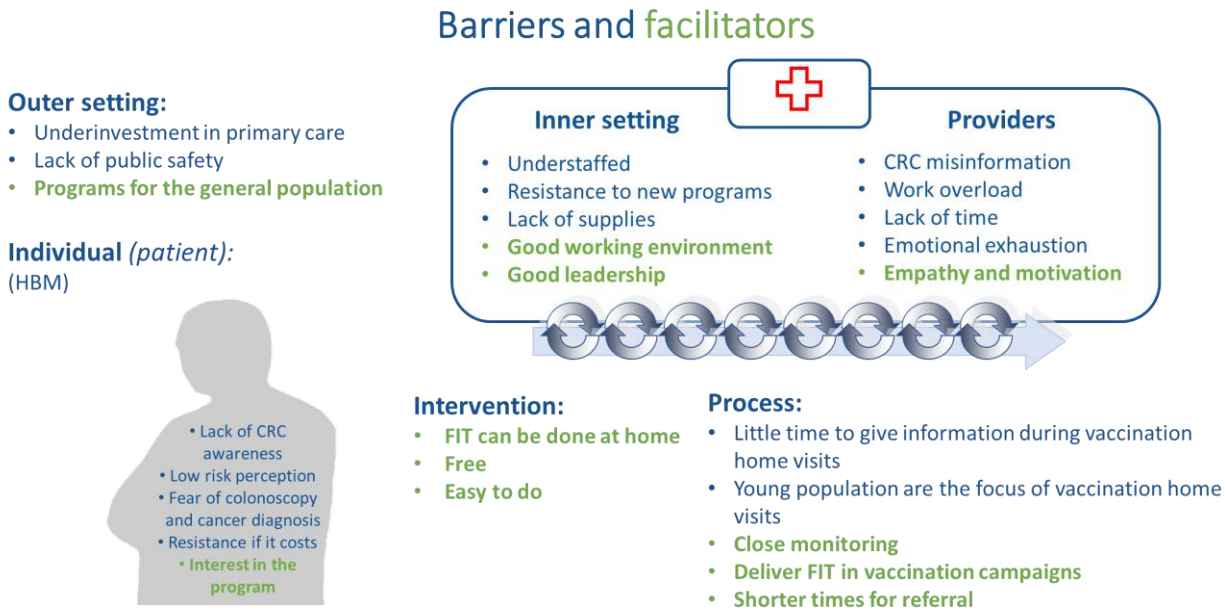


Figure 1.1. Main barriers and facilitators identified across the Consolidated Framework for Implementation Research (CFIR) domains.

Barriers are shown in blue. Facilitators in green. CRC: Colorectal cancer. HBM: Health Belief Model. The HBM was used for the Individual (patient) level. Adapted from: Damschroder LJ, Aron DC, Keith RE, et al: Fostering implementation of health services research findings into practice: A consolidated framework for advancing implementation science. Implementation Science, 2009. [19,20]

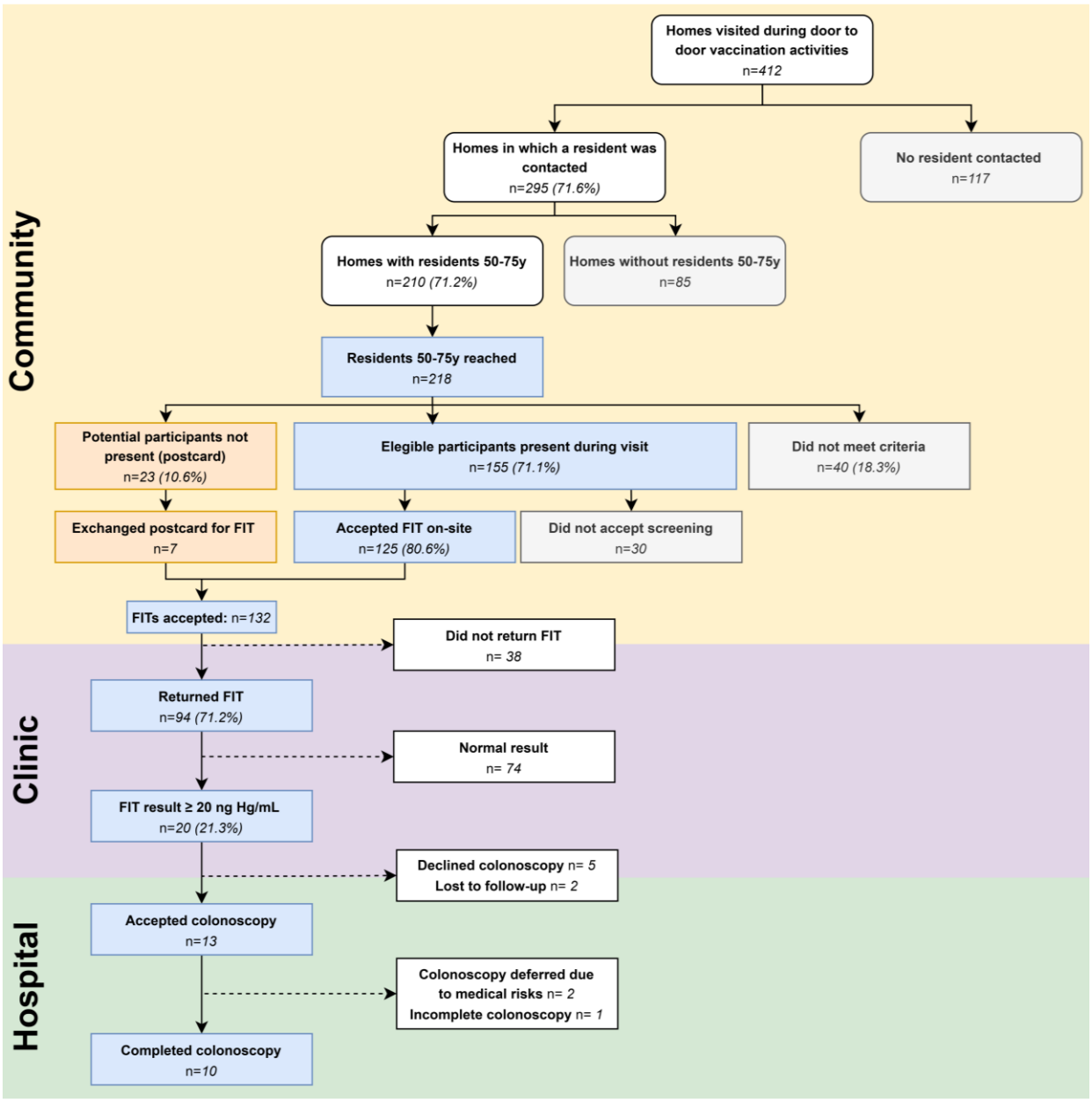


Figure 1.2. Flow of participants in a colorectal cancer screening study paired with door-to-door vaccination activities in Mexico City, 2020.

Table 1.1. Characteristics of 132 study participants enrolled in a colorectal cancer screening study paired with door-to-door vaccination activities in Mexico City, 2020.

	n	(%)
Age (SD)	62.0 (6.8)	
Gender, n(%)		
Male n(%)	48	36.4%
Female n(%)	84	63.6%
Mean BMI (±SD), kg/m2	28.9 (5.5)	
Educational attainment*, n(%)		
None	10	7.6%
Less than high-school	78	59.1%
High-school / Vocational	29	22.0%
Bachelor	14	10.6%
Graduate	1	0.8%
Health insurance, n(%)		
IMSS	75	56.8%
Seguro Popular / INSABI	28	21.2%
Defensa o Marina	1	0.8%
No affiliation	16	12.1%
ISSSTE	8	6.1%
Other	3	2.3%
Private Insurance	1	0.8%
Diabetes, n(%)	42	31.8%
Tobacco smoking, n(%)		
Past	46	34.8%
Never	58	43.9%
Current	28	21.2%

SD: standard deviation; IMSS: Instituto Mexicano del Seguro Social. INSABI: Instituto de Salud para el Bienestar. ISSSTE: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado.
*Highest level of education completed;

Table 1.2. Pathology results of participants with abnormal FIT (≥20 ng Hg/ml) who completed colonoscopy (n=10).

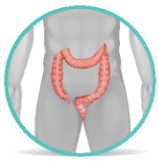
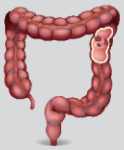
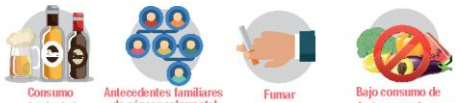
FIT result	Quality of preparation, Boston scale[23]	Procedure duration (mins)	Hemorrhoidal disease	Diverticular disease	Other benign disease	Number of polyps	Tubular Adenoma	Hyperplastic	Chronic colitis	Recommended follow-up
80	9	25	-	-	-	2	-	2	-	10 years
68	9	25	-	-	-	10	1 (low grade)	-	4	7 years
65	8	15	-	-	-	1	1 (low grade)	-	-	1 year
60	6	10	-	✓	-	1	1	-		7 years
32	8	20	-	-	-	2	-	2	-	10 years
25	6	10	-	-	✓	6	4 (low grade)*	-	-	5 years
21	9	18	-	✓	-	-	-	-	-	10 years
21	8	35	-	-	✓	5	3 (low grade)*	-	2	4 months**
20	7	20	✓	✓	-	3	-	2	1	10 years
20	9	25	-	-	-	-	-	-	-	10 years

FIT: fecal immunochemical tests. FIT results units are nanograms of hemoglobin/ml.
*Classified as high risk, since there were 3 or more adenomas found. [25]
**Gastroenterologist requested procedure to be repeated with better bowel preparation

Table S1.3. Initial and final versions of educational materials developed.

INITIAL VERSION	FINAL VERSION
Poster	
	
Postcard	
	

INITIAL VERSION	FINAL VERSION
	
Brochure	
	

INITIAL VERSION	FINAL VERSION
# ¿Qué sabes del cáncer colorrectal?  ## Impacto en México • Cuarto lugar de muertes por cáncer • Primera causa de muerte por cáncer en la Ciudad de México • El colon también se conoce como **intestino grueso.** • El colon es la **última sección del sistema digestivo.** • **El recto es la parte final del colon.** • **El sistema digestivo se encarga de aprovechar los nutrientes** que se encuentran en alimentos y bebidas.  ## ¿Cómo se origina? • El cáncer **puede presentarse en cualquier parte** del colon y del recto. • Casi todos los casos tienen su origen en un pólipo, el cual es **un crecimiento anormal de células** en el interior del colon. • **El adenoma** es el tipo de pólipo que más frecuentemente se convierte en cáncer. • Los pólipos **pueden crecer durante años** hasta convertirse en un tumor canceroso. • No todos los pólipos son iguales, **algunos son más propensos a convertirse en cáncer que otros.** • **Su crecimiento es lento,** esto permite que los médicos encuentren pólipos o cáncer etapas tempranas e inicien tratamiento adecuado. 1	# ¿Qué sabes del cáncer colorrectal?  ## Impacto en México • Cuarto lugar de muertes por cáncer • Primera causa de muerte por cáncer en la Ciudad de México • El **colon** es la última sección del sistema digestivo. • El colon también se conoce como intestino grueso. • El recto es la parte final del colon.  ## Cáncer colorrectal • Este cáncer puede presentarse en cualquier parte del colon. • Comienza como un pólipo, que es un tumor benigno que se forma en el interior del colon.  • **El crecimiento de los pólipos es lento,** (de años) lo que permite tratarlos antes de que se conviertan en cáncer. 1
## Factores de riesgo Existen factores que aumentan la probabilidad de desarrollar una enfermedad, como conductas, características y exposiciones. Los factores que aumentan el riesgo de desarrollar cáncer colorrectal son:  • Tener más de 50 años • Antecedentes familiares de cáncer de colon o pólipos • Enfermedades que inflaman el intestino, como colitis ulcerosa y enfermedad de Crohn • Comer muchas grasas animales, carnes rojas y procesadas • No hacer ejercicio • Obesidad • Diabetes • Consumir tabaco • Tomar bebidas alcohólicas en exceso • Comer pocas frutas y verduras ## Síntomas Desafortunadamente muchas personas **no tienen ninguna señal ni molestia hasta que la enfermedad ya es avanzada.** Los más frecuentes son:  • Cambios en la consistencia de las heces o en los hábitos para ir al baño por más de 4 semanas • Molestias persistentes como gases, calambres o dolor • Debilidad o fatiga • Sensación de no vaciar los intestinos • Adelgazamiento sin causa aparente • Sangrado rectal o sangre en las heces (en casos avanzados) Los síntomas pueden ser diferentes según el tamaño y ubicación del tumor. 2	## Factores de riesgo Aumentan la probabilidad de que a una persona le dé cáncer colorrectal:   ## Síntomas Desafortunadamente esta enfermedad **no suele dar molestias hasta que está avanzada. Los más frecuentes son:**   2

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Tratamiento

Sin atención apropiada, el cáncer de colon puede complicarse.

La cirugía es el principal tratamiento.

- Cuando se ha identificado dónde está el tumor, **se corta la sección afectada y algunos centímetros más** a los extremos del intestino.
- El tipo de cirugía y qué tanta cantidad de colon debe extirparse **dependerá de la localización del tumor** y de la presencia o no de complicaciones asociadas.

Detección temprana

El Instituto Nacional de Cancerología y la Secretaría de Salud recomiendan a hombres y mujeres **a partir de los 50 años de edad:**

Realizarse una **prueba FIT** para encontrar sangre oculta en heces

Una colonoscopía para la detección temprana de **pólipos o cáncer**

La prueba FIT tiene un precio en el mercado de 200 a 400 pesos, mientras que la colonoscopía alcanza un costo de entre 6 mil y 14 mil pesos.
Sin embargo, **los participantes en este estudio podrán tener acceso a ellas de forma totalmente gratuita.**

Con la detección temprana **hay más del 95% de probabilidades de cura.**

¡El cáncer colorrectal es prevenible!

Detección temprana

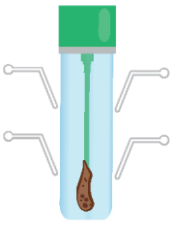
La Secretaría de Salud recomienda que **a partir de los 50 años de edad,** hombres y mujeres se realicen

Actualmente en el centro de salud México España se está brindando la prueba FIT de forma gratuita como parte de un programa piloto.

Si tienes más de 50 años, ¡acude a solicitarla!

Prueba fecal

- Es **rápida y fácil** de realizarse.
- **Se entrega en el Centro de Salud** para que la envíen a un laboratorio a ser analizada.



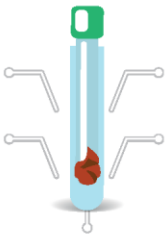
- Solo requiere de una **pequeña muestra** de popó.
- **Si la prueba es anormal, significa que hay sangre en el excremento.** No hay que alarmarse.
El siguiente paso es hacerse una colonoscopía.

Existen muchas causas para presentar sangre en el excremento, el cáncer es sólo una de ellas

Para la prueba FIT, el paciente solo debe tomar 1 pequeña muestra de su excremento en la comodidad de su casa. Hacerlo es muy sencillo.

Prueba FIT

- Es **rápida y fácil** de realizarse.
- **Existen proyectos** que ofrecen las pruebas **FIT sin costo.**



- Solo requiere de una **pequeña muestra** de heces.
- **Se entrega en el Centro de Salud** para que la **envíen a un laboratorio** a ser analizada.

- **Si la prueba FIT es positiva,** no hay que alarmarse.
El siguiente paso es hacerse una colonoscopía.

Existen muchas causas para presentar sangre en heces, el cáncer es sólo una de ellas.

Para la prueba FIT, el paciente solo debe tomar solo 1 pequeña muestra de su excreción en la comodidad de su casa. Hacerlo es tan sencillo como los pasos a seguir:

1.	Anote en la prueba su nombre completo, fecha de nacimiento y la fecha en que tome la muestra.
2.	Coloque papel higiénico o papel de cocina sobre la taza del baño, para recolectar la muestra, evitando que no entre en contacto con el agua.
3.	Deposite la muestra de materia fecal encima del papel. Para facilitar la toma, colóquela junto con el papel en una caja o plato de cartón limpio, que deberá tirar al final.
4.	Retire la tapa del dispositivo recolector girando y levantando. El bastón del frasco recolector está unida a la tapa.
5.	Tome la muestra con el palito del frasco recolector. Solo la punta del bastón debe estar cubierta con materia fecal.
6.	Devuelva el palito al frasco recolector. Cierre bien el contenedor y agítelo para que el líquido en su interior se mezcle con la materia fecal. Y no reabra el frasco.
7.	Finalmente lleve de inmediato el recolector con la muestra al centro de salud indicado.

¿Cómo hacer la prueba FIT?

Paso 1

IMPORTANTE
No olvides escribir en la etiqueta del tubo, tu nombre y la fecha en que tomaste la muestra.

Paso 2

Coloca una pequeña cantidad de popó sobre un papel, cartón o recipiente, de manera que no toque el agua de la taza del baño ni la orina.

Paso 3

Abre el tubo, saca el palillo y mete 9 veces la punta (que parece un tornillo) dentro de la popó.

Paso 4

Una vez tomada la muestra, vuelve a meter el palillo dentro del tubo y ciérralo bien. Guárdalo en un lugar fresco y seco.

Paso 5

Tira el resto de la popó en el excusado.

Paso 6

Entrega el tubo con tu muestra en el Centro de Salud en menos de 3 días. Se enviará para análisis de laboratorio.

Paso 7

Si la prueba resulta anormal, significa que se detectó sangre en el excremento.
Para saber la causa del sangrado, es necesario hacerse un examen completo del colon, llamado colonoscopía.

Con la detección temprana
¡El cáncer colorrectal es curable!

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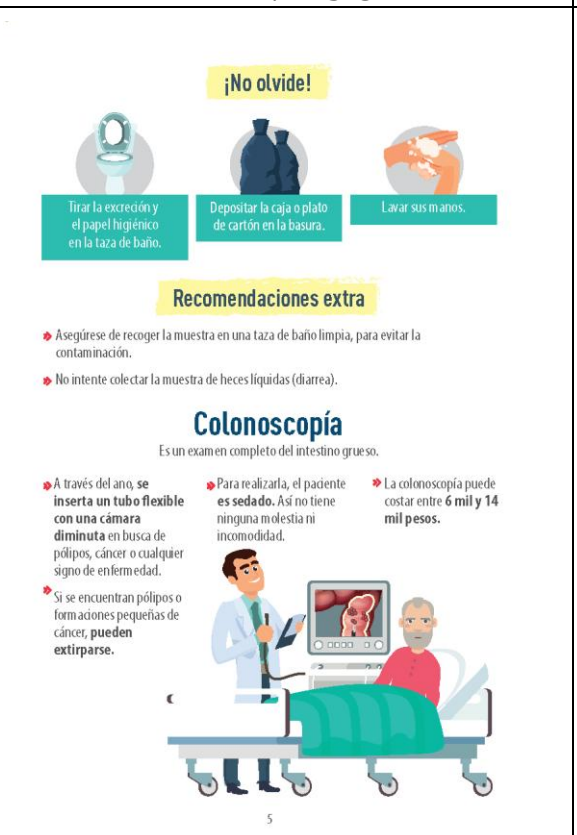	
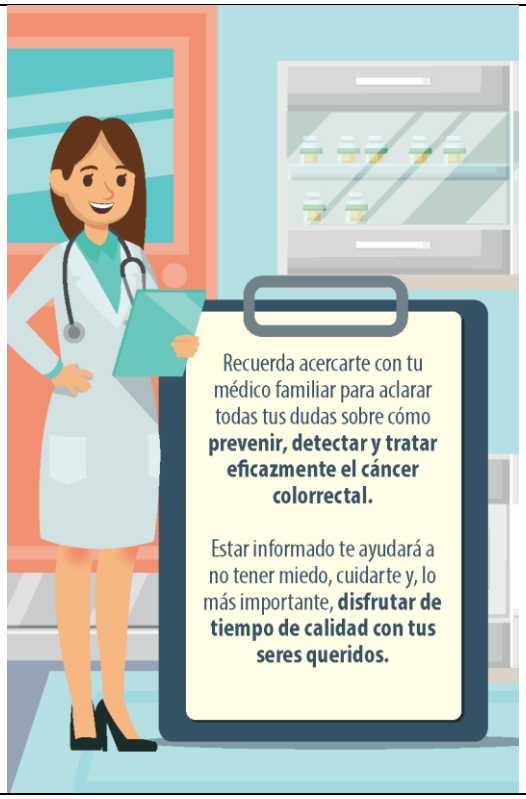	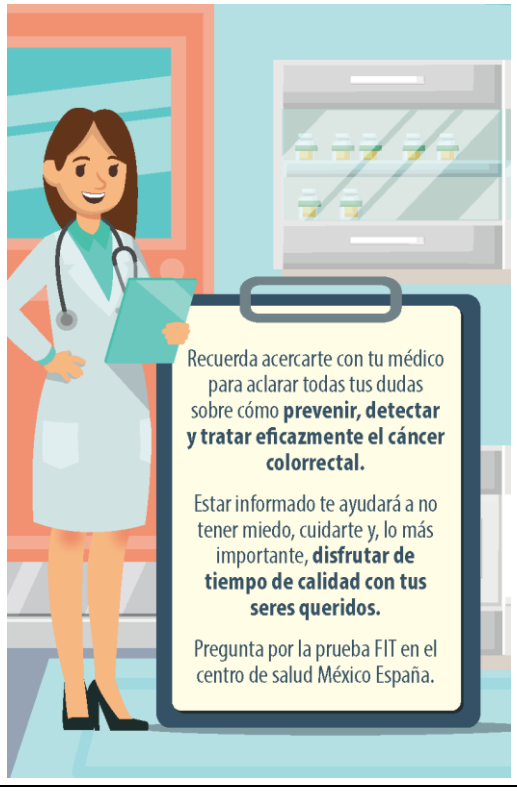

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CHAPTER 2. FEASIBILITY OF COLORECTAL CANCER SCREENING IN AN INTEGRATED HEALTHCARE SYSTEM IN NUEVO LEON, MEXICO

Introduction

Colorectal cancer (CRC) is preventable and curable with screening and early detection.[1] In 2021, CRC was Mexico's second most common cause of cancer mortality (8.5 deaths per 100,000) in both sexes.[10] The CRC documented mortality rate in Mexico has rapidly increased over the last two decades,[4] especially in urban areas.[6] Currently, with no organized colorectal cancer screening programs in Mexico, CRC is often diagnosed at advanced stages.[13] Given the relatively low cost of fecal immunochemical tests (FIT) and the increasing number of trained endoscopists and other specialists in Mexico, the introduction of population-based CRC screening and treatment programs within many of Mexico's integrated health systems is possible.[39,50]

CRC screening is a complex multistep process, especially in settings inexperienced with screening or where resources may be constrained.[51,52] In Mexico, new CRC screening programs will be required to include education about CRC risk and CRC screening for both health workers and the general population. Health systems will need to implement patient outreach and navigation strategies to encourage high levels of patient participation and completion of necessary steps from screening to diagnosis.[53,54] These strategies have not previously been developed for and tested in integrated healthcare systems that provide care to most of the general population in Mexico.

The Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado de Nuevo Leon (ISSSTELEON) is a publicly funded insurance plan, healthcare provider, and pension fund manager for all state and municipal civil workers and their families in Nuevo Leon, Mexico. In the absence of its own CRC screening program, ISSSTELEON reported an average of 10 cases

of CRC per year from 2020-2022, mostly at symptomatic and advanced stages of disease. ISSSTELEON does not provide routine CRC screening to its members, but it does have its own diagnostic endoscopy unit, which serves high-risk and symptomatic patients, and a full range of services to provide CRC treatment when it is diagnosed. In addition, ISSSTELEON has experience with cancer screening already, having implemented screening programs for breast and cervical cancer. In 2022, its leaders expressed interest in partnering with our research team to develop and test the feasibility of a CRC screening program for its average-risk patients between the ages of 50-75.

The goal of this study, therefore, was to prepare for the implementation of a comprehensive CRC screening program at ISSSTELEON by: 1) developing a model for comprehensive screening for ISSSTELEON, 2) testing the feasibility and effectiveness of core components of the model (i.e., patient recruitment, education, and reminders to complete FIT and colonoscopy when needed), and 3) documenting adaptations made to the initial model of CRC screening, with recommendations that have implications for ISSSTELEON and other health systems in Mexico that are considering the implementation of comprehensive CRC screening programs.

Methods

Program setting

ISSSTELEON is an integrated healthcare system in the state of Nuevo Leon, Mexico. We conducted the study at ISSSTELEON's Centro Medico, its largest medical center in the capital city of Monterrey, which in 2022 served a population of 59,270 individuals, including state government employees, retirees, and their family members. Centro Medico employs 36 primary care physicians and as described above, has established its own endoscopy unit and pathology laboratory, as well as surgical and oncology services for the diagnosis and treatment of CRC.

ISSSTELEON uses an electronic health record (EHR) to document all services, record laboratory results, and record referrals between specialists. ISSSTELEON also has a call center that employs 28 individuals who manage patient telephone outreach, three of whom were assigned to this study. ISSSTELEON's EHR includes a patient portal that it uses to communicate directly with patients through a mobile phone app.

Target Population

In 2022, ISSSTELEON's Centro Medico served 9,850 adults between the ages of 50-75, the proposed age for CRC screening in Mexico. For this study, our target population was adults aged 50-75 of average risk (i.e., with no personal or family history of colorectal cancer in a first-degree relative, and no recent history of active rectal bleeding).

To understand how different population subgroups served by ISSSTELEON would respond to the screening program, a sample including 150 active workers (75 with an at-work clinic, 75 without) and 150 retired workers was invited. The invited patient sample was selected by the ISSSTELEON informatics department using administrative records. They sorted administrative records randomly for each group to be invited and selected the records in order until they met the sample quota (first 75 active workers with an at-work clinic, first 75 active workers without an at-work clinic, and first 150 retirees). One duplicate was identified in the active worker group, and consequently, the total number of policyholders invited to the study was 299.

Design of screening intervention. We created a CRC Screening Task Force, composed of members of the research team and members of the medical leadership and quality improvement divisions at ISSSTELEON. Activities included weekly meetings over 18 months, during which evidence-based strategies to provide screening and diagnostic follow-up were reviewed, selected, and

tailored to local resources. Specifically, we reviewed the design used in our pilot study in Mexico City in 2019[55] (Chapter 1) and the evidence of effectiveness of interventions for CRC screening recommended by the U.S. Community Preventive Services Task Force (Community Guide).[56–59] We assessed the potential feasibility of their implementation in the context of local resources and healthcare processes at ISSSTELEON and other health systems in Mexico. We focused on approaches for outreach in the context of an integrated health system, including emails, automated phone calls, and participant navigation to receive FIT. This process included the development of detailed workflows and systems to record drop-offs in participation at each step of the screening process and electronic health record reporting systems to evaluate clinical outcomes. Implementers, which included two primary care physicians, three call center agents, a gastroenterologist, the laboratory director, the information technology director, and the director of communications, were actively engaged in all design processes. We also developed a protocol for follow-up of abnormal FIT results using patient navigation to ensure completion of colonoscopy and necessary services for diagnosis and treatment.

Adaptation of evidence-based education materials and patient navigation tools

Educational Materials and Scripts. A brochure, poster, video, and postcard developed in our pilot study in Mexico City in 2019[55] were shared with ISSSTELEON's Communication team. The Communication team adapted the materials to the local context (variations of language, logos, addresses & phones) (**Supplemental Table S2.5**). After local IRB review and in response to their requests, some sentences in the educational materials were rephrased. ISSSTELEON's call center personnel reviewed and adjusted proposed scripts for automated calls to educate and invite participants for screening. Through a literature search, we identified an evidence-based telephone counseling script, based on the Transtheoretical Model of Behavior Change, that was developed

for a CRC screening study conducted in Spanish in the United States, and we adapted it for use as a navigation guide for ISSSTELEON.[60,61] Call center personnel reviewed and further adjusted the proposed navigation guide to support participants through the CRC screening process.

Outreach and recruitment.

Recruitment activities began in May 2023 and concluded in October 2023. Training of study staff in study procedures was conducted by ISSSTELEON's quality department, with support from our research team. During this training, all implementers were presented with the study objectives, timeline, and detailed protocol instructions, encompassing all study procedures, materials, documentation practices, and ethical principles of human subjects research. Furthermore, we informed all healthcare staff about the study objectives and procedures that would be carried out during the following months.

Participants were contacted first by email, with a message providing study information and online access to the educational materials. The email also included an invitation to schedule an appointment at the medical center (i.e., for retirees and active workers with no on-site medical office) or the medical office at their workplace (i.e. for active workers only) to continue the recruitment process. Participants who did not respond after two weeks of receiving the email received an automated telephone call with a recorded message inviting them to enroll. Participants who did not respond within two weeks of the call received a telephone call from a patient navigator, trained to explain the screening process, invite the patient to attend an in-person screening appointment and identify and address potential patient-level concerns or logistical barriers to screening as needed.

During the screening appointment, which took place either at their work-site medical office, or at the medical center, a trained primary care physician used educational materials to

explain what the CRC screening program consisted of, verified that the participant met the eligibility criteria for CRC screening, obtained informed consent, and provided a FIT kit (OC FIT-CHEK, Polymedco, quantitative test). Participants were informed that they should return the FIT kit within the week at the work-site medical office or the medical center. When the study was set to conclude, call center personnel made an additional reminder call to participants who had not yet returned their FIT kit. Participants were considered lost to follow-up if three consecutive contact attempts by the call center were unsuccessful.

Follow up after FIT completion

Test results were delivered to participants via a secure mobile phone app as soon as they were available. Results were also made available to their primary care doctor through the EHR. Participants with a normal FIT result (defined as <20ng hemoglobin (Hg) per mL) received their results through their mobile app and from their primary care doctor during their next visit. Participants with abnormal FIT results were contacted by telephone by trained call center personnel to inform them of the result obtained and its meaning. Call center personnel notified participants that a colonoscopy was required to identify the cause of the presence of hemoglobin in feces, explained the process, and scheduled an appointment with the gastroenterology department to arrange a colonoscopy. The endoscopy unit nurse delivered the bowel preparation solution and instructions to all participants during this visit. Participants received a telephone reminder one day prior to the intake visit and one day prior to the colonoscopy. Participants received a preliminary report from the endoscopist immediately after the completion of the procedure. When needed, tissue samples were sent to pathology, and results were delivered to the patient by the performing endoscopist, who explained the results and recommended surveillance per standard colonoscopy surveillance guidelines.[22]

Monitoring and evaluation

ISSSTELEON's quality department monitored patient follow-up status throughout the screening process. They identified and tracked steps of the process where study participants either continued or discontinued their participation or became unreachable, allowing for a detailed and thorough understanding of participant retention and attrition patterns. These patterns are presented visually using a Sankey diagram (SankeyMATIC[62]), to emphasize the flow of participants over time. Participants' characteristics (age and sex) and usage of medical services (number of healthcare interactions in the previous 12 months and of days since their last appointment) were obtained by ISSSTELEON from the EHR and shared as de-identified data for analysis. Participants and follow-up characteristics are shown as mean (standard deviation) for continuous variables and as frequencies and proportions for categorical variables. Participants were classified into five outcome groups: (1) Not able to contact, (2) Excluded from the study, (3) Declined to participate, (4) Lost to follow up and (5) Received and returned FIT. All adaptations were documented using the Framework for Reporting Adaptations and Modifications-Expanded (FRAME).[63] This Framework was developed to systematically document adaptations and modifications made to evidence-based interventions. Elements of reporting include when and what was modified, the level of delivery, the nature, goal, and reasons for change, and who participated in the decision to modify.

The final versions of the study protocol, educational materials, reminders, and navigation guides were reviewed and approved by Institutional Review Boards (IRB) at Mexico's Instituto Nacional de Salud Publica and ISSSTELEON. UCSF's IRB approved this study as exempt with protocol number 24-42435.

Results

The mean age of the 299 policyholders invited was 60.1 (SD 8.3), 62.5% (n=187) were male, and their average number of healthcare interactions (visits to any department, i.e. primary care, emergency room, etc.) in the previous year was 12.3 (SD 12.6). Seven patients were ineligible due to personal history of colorectal cancer or no active coverage (no longer employed or covered by local government). Of the 292 participants who were attempted to be contacted, 49% (142/292) scheduled a first appointment after being invited. Response to outreach approaches was similar for active workers and retirees, with the most effective outreach approach being navigation, with 117 out of the 209 policyholders (56%) contacted through a live navigation call and scheduling a recruitment appointment. Attendance to the recruitment appointment and accepting FIT was also similar in active workers and retirees. In the recruitment appointment, 10 declined to participate, 9 met an exclusion criterion and 92/111 (83%) accepted a FIT kit.

Detailed participant and follow-up characteristics by type of policyholder are shown in **Table 2.1**. The mean age for the population that accepted a FIT was 59.7 (SD 7.0) years, and 64.1% (59/92) were male. Of these, 80/92 (87%) returned their FIT kit, and 8/80 (10%) had an abnormal FIT requiring referral for colonoscopy. FIT return rate was higher among active workers, while FIT positive rate was higher among retirees. Five colonoscopies (5/8) were performed, and in all 5 colonoscopies performed, polyps were removed. Pathology results reported advanced adenomas in three. Three participants did not go through colonoscopy, one due to high anesthetic risk and two because they did not accept the procedure. They were referred to the Gastroenterology department for a follow-up appointment to discuss implications and follow-up alternatives.

Overall, 80 out of 292 patients targeted by the intervention ultimately completed FIT, 8 tested positive, and of these 5 completed colonoscopy as recommended. **Figure 2.1** shows

participant retention and attrition patterns. Drop-offs were identified at 1) participant invitation, 2) attending recruitment appointment (no-shows that required second navigation and scheduling a new appointment), and 3) FIT return. The biggest losses of participants were due to participants declining participation in the study (n=64) and lack of success in making contact with prospective participants (n=58). Among participants who received navigation and showed interest in being screened, 73 received a second navigation call, which resulted in 22 new recruitment appointments scheduled. Participants attended 13 of these new appointments. Throughout the study, there were a total of 53 recruitment appointments that participants did not attend.

Table 2.2 shows the proportion of invited individuals by follow-up outcome of the screening process. Outcomes were similar for both active workers and retirees. Around two-thirds of patients in each group could either not be reached, declined to participate, or did not follow up after agreeing to participate. **Table 2.3** shows that patients who followed through and completed FIT seemed to have a slightly higher number of interactions with the clinic in the past, while participants who declined or were not able to be contacted had the fewest interactions with the clinic.

Adaptations

A total of 21 adaptations were documented, as presented in **Table 2.4**. 67% (n=14) were proactive during pre-implementation and planning, while the rest (n=7) were reactive during implementation. The most common modifications were related to the context, specifically the personnel that was performing an activity (48%), followed by format (43%). Most modifications involved adding elements (33%), while the most common adaptation goals were to increase reach or engagement (33%), followed by improving feasibility (29%). The most common rationales for the modifications were at the organization level and due to available resources (57%). The Health

Services Director was the most common individual to make an ultimate decision to make a modification (52%). However, most modifications involved discussion among different individuals involved in aspects of the implementation process, with 71% of them involving 3 or more. The individuals who participated in most of the decisions to modify were the individual practitioners who delivered the intervention (90%), followed by the Health Services Director (81%). Detailed information on the adaptations and selected evaluated components are shown in the **Appendix**.

Discussion

Our study shows that implementing CRC screening using an adapted model could be feasible in integrated health systems in Mexico such as ISSSTELEON. Around half of the invited policyholders, none of whom had ever been exposed to CRC screening, scheduled a first appointment, with live navigation calls being the most effective outreach approach. FIT uptake and return were high among participants who could be reached and offered a FIT kit in person, and, though no cancers were detected in this small sample, all completed colonoscopies resulted in polyp detection and removal. Adaptations were made to the CRC screening process before and during the intervention and were mostly driven by collaborative decision-making to increase participant reach and feasibility within the context of existing clinical resources and protocols.

Compared to evidence-based CRC screening programs listed by the National Cancer Institute[64] with similar approaches (letters, automated phone calls, or navigation), our study yielded similar screening uptake at in-person recruitment (83% vs. 80.5%)[65] and higher FIT return (87% vs. 72%).[65] Considering crude screening, our approach yielded a similar percentage (27%, 80/292), compared to 24% found when using letter and automated calls[66], 21.5% found with a letter and a personal call[67], and 22.5% after telephone contact in other contexts.[68] Our observed

percentage of participants who declined participation (64/292, 22%) was higher compared to other studies (10%)[65], while the percentage that we were not able to contact (53/292, 18%) was lower to other studies (52%).[69] These results could be due to this population never being exposed to this type of screening before, and to the contact information being updated relatively frequently since ISSSTELEON also provides financial services to policyholders, respectively. Additionally, our results are comparable to what has been observed in other studies previously conducted in Mexico, including our observed 87% FIT return[38,39], and our 10% FIT positivity compared to the 91% and 15.2%, respectively, observed in Mexico City with the same cutoff (≥20ng Hg/mL).[39]

Involving different implementers in decision-making related to program adaptation fosters discussion and consensus, allowing interventions to align with diverse professional values and perceived needs of different actors, which has been found to be ultimately associated with implementation success.[70,71] In our study, individuals involved in the different aspects of the implementation process within the health system participated in all the discussions and final decisions on the adaptations and modifications of the intervention. Most of these adaptations were made by three or more actors, and notably, although the Health Services Director made the ultimate decision in many cases, the individual practitioners and implementers were empowered to make many final decisions regarding the intervention. This reflects how this healthcare system promotes and ensures collaboration across all levels of the team hierarchy, with the purpose of maximizing the odds of implementation success.

In Mexico in 2020, integrated healthcare systems provided care to 61% of the national population.[72] Our results can help guide the development of activities within these health systems that can lead to successful CRC screening programs nationally. Our adaptation process, documented adaptations, and retention and attrition patterns can serve as a foundation for creating

tailored interventions that meet the specific needs of these healthcare systems with different resources and patient populations. Since screening programs that address barriers at multiple levels and steps in the screening process have been shown to improve screening rates and be cost-effective[73,74], having methods to identify the specific steps and levels with high attrition that need adaptations is key to improving programs and their effectiveness across health systems in Mexico. Tracking retention and attrition patterns through a Sankey diagram can be a useful tool to identify these drop-offs so adaptations can be tailored to increase participation. In our study, we identified challenges at 1) participant invitation (having to schedule an appointment and pick up the kit at the Medical Center), 2) attending recruitment appointment (no-shows that required a second navigation and scheduling a new appointment), 3) FIT return (participants that had not returned it required a reminder phone call), and 4) colonoscopy (participants required navigation encouraging completion of colonoscopy).

Considering our experience in this study, our recommendations for future screening programs include: tailoring educational materials for the local context; allowing enough time for the first one-on-one education interaction, since it will be the first time hearing about CRC screening for most of the population; if there is an interaction before in-person recruitment, adding inclusion and exclusion criteria evaluation before a visit to avoid delay in referral to high-risk screening process and identify participants who may not be able to tolerate colonoscopy; simplifying the process by consolidating processes and procedures during the same visit; tracking drop-offs throughout the process to tailor adaptations that address step-specific barriers; and integrating all implementers in decision-making to anticipate system barriers and address them before implementation.

This study was the first attempt to introduce average-risk FIT-based CRC screening in an integrated health system in Mexico with resources to provide care across the cancer continuum beyond the initial screening process. Additionally, the effectiveness of email, automated phone calls, and navigation as outreach strategies for colorectal cancer screening has not been tested before in Mexico. In addition, our development of detailed workflows and systems to record drop-offs in participation allowed us to identify steps of the screening process where participants were lost. Finally, we systematically tracked and registered all the adaptations and modifications made to the screening program using FRAME, allowing a better understanding of the needed changes to integrate CRC screening into integrated health systems in Mexico.[63]

Limitations in our study include a small sample size and the fact that the research team engaged with the healthcare team and patients in ways that may not reflect real-world conditions. For example, the process of informed consent for research purposes could have influenced the rate of participation in ways that would not be seen in real-world conditions. Nevertheless, we believe these limitations do not hinder the significance, interpretation, and potential reproducibility of our results within other integrated health systems in Mexico.

Although our study showed promising results, there are aspects of CRC screening in this context that require further investigation. These include: 1) increased understanding of the barriers participants faced at each drop-off in participation throughout the process; 2) improved outreach strategies among populations without up-to-date contact information; 3) assessments of the effectiveness of CRC screening on a larger population at ISSSTELEON; 4) identification of the most effective FIT return support approaches for this context; and 5) understanding the reproducibility of these results in other integrated health systems in Mexico.

Conclusion

In this study, we identified that navigation as an outreach approach for participant recruitment, followed by one-on-one education by a trained primary care physician at recruitment, along with adaptations being driven by collaborative decision-making can make a CRC screening program feasible and successful within an integrated health system in Mexico.

Funding

This work was supported by an intramural grant from the UCSF Global Cancer Program (Resource Allocation Program award)

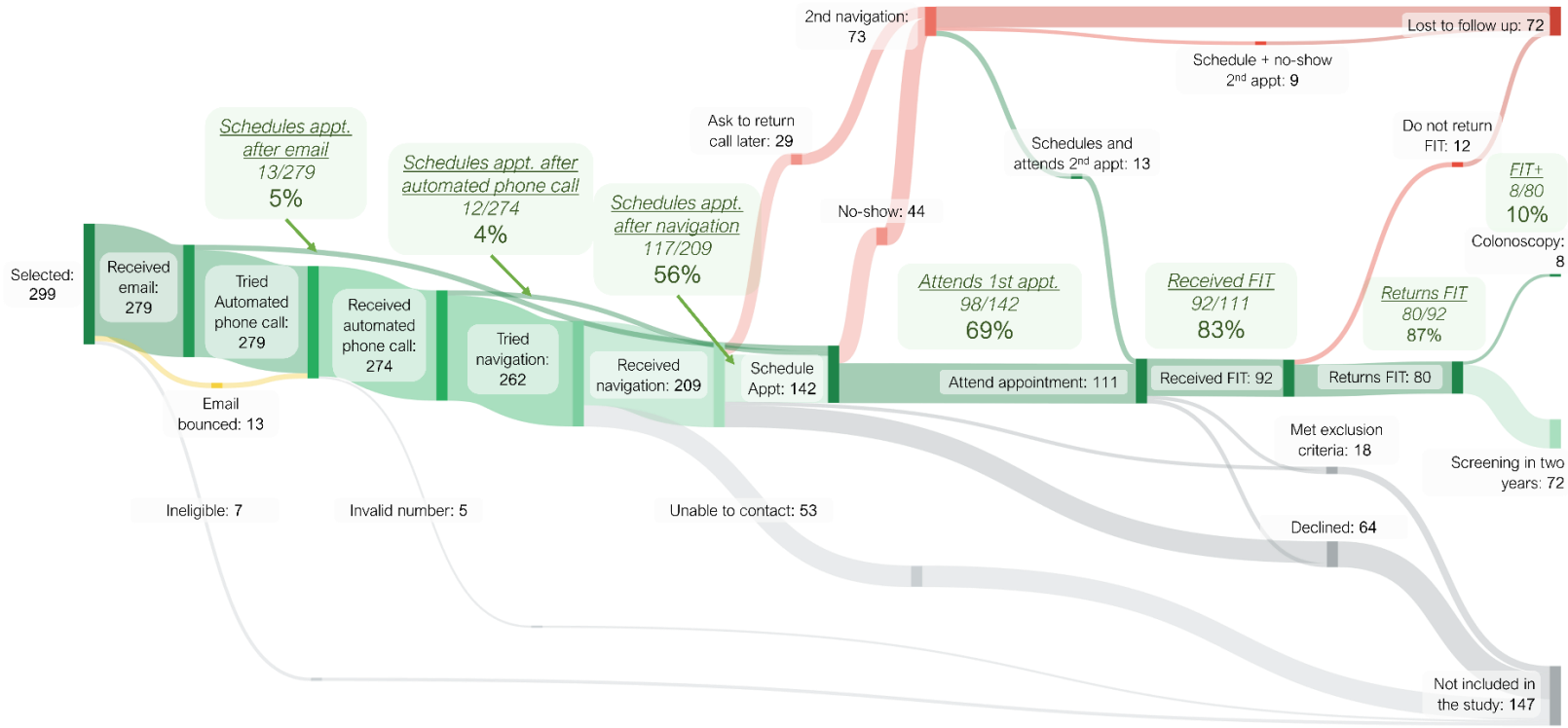


Figure 2.1. Flow of 299 ISSSTELEON participants throughout the colorectal screening process.

Green flow represents the optimal process of patient flow throughout the CRC screening process. Red flow represents pathways that led to a loss of follow-up where patients did not complete screening after declaring interest in CRC screening. Gray flow represents pathways that led to patients not being included in the study.

Table 2.1. Characteristics of invited participants and proportion completing each step of the screening process.

	Active Workers (n=149)	Retirees (n=150)	**Overall (n=299)**
Participants' characteristics			
Age, (SD)	57.2 (7.7)	63 (7.9)	60.1 (8.3)
Male, n (%)	96 (64.4)	91 (60.7)	187 (62.5)
Average healthcare interactions in the last year, (SD)	11.3 (11.8)	13.3 (13.3)	12.3 (12.6)
Average days since last appointment, (SD)	69.3 (81.1)	56.1 (64.3)	62.7 (73.3)
First contact and scheduling recruitment appointment (RA)			
Schedules RA after email, n (%)*	8 (5.6) *8/144*	5 (3.7) *5/135*	13 (4.7) *13/279*
Schedules RA after automated phone call, n (%)*	5 (3.7) *5/135*	7 (5) *7/139*	12 (4.4) *12/274*
Schedules RA after navigation, (%)*	60 (57.1) *60/105*	57 (54.8) *57/104*	117 (56.0) *117/209*
Recruitment and follow-up			
Attends RA, n (%)*	56 (76.7) *56/73*	55 (79.7) *55/69*	111 (78.2) *111/142*
Accepts FIT, n (%)*	46 (82.1) *46/56*	46 (83.6) *46/55*	92 (82.9) *92/111*
Returns FIT, n (%)*	42 (91.3) *42/46*	38 (82.6) *38/46*	80 (87) *80/92*
Average days to FIT return	17.5 (22.2)	15.3 (19.5)	16.4 (20.7)
Positive FIT result, n (%)*	3 (7.1) *3/42*	5 (13.2) *5/38*	8 (10) *8/80*

RA: Recruitment appointment; FIT: fecal immunochemical test.

* Numbers below percentages show the numerator and denominator used to calculate each. Denominators for each specific stage of screening mostly depend on results from the previous step. Denominators for each stage are defined as follows: denominators for scheduling RA after email, are the participants that received the email (not bounced); for scheduling RA after automated phone call are participants that received the automated phone call; for scheduling RA after navigation are participants that received navigation; for attending RA are participants that scheduled a RA; for accepting FIT are participants that attended RA; for returning FIT are participants that accepted FIT; and for positive FIT result are participants that returned FIT.

Table 2.2. Distribution of follow-up outcome by type of participant for all invited participants (n=299).

Group	Active Workers (n=149)	Retirees (n=150)	**Overall (n=299)**
Not able to contact*, n (%)	27 (18.1)	31 (20.7)	58 (19.4)
Excluded**, n (%)	10 (6.7)	15 (10)	25 (8.4)
Declined, n (%)	28 (18.8)	36 (24)	64 (21.4)
Lost to follow-up***, n (%)	42 (28.2)	30 (20)	72 (24.1)
Received and returned FIT, n (%)	42 (28.2)	38 (25.3)	80 (26.8)

FIT: fecal immunochemical test.
*Invalid phone number, or not able to be contacted by the call center
**No longer employed in local government, or met at least one exclusion criteria
*** Did not return FIT; scheduled recruitment appointment and were no-shows; received navigation twice but did not schedule an appointment.

Table 2.3. Participant characteristics by follow-up outcome.

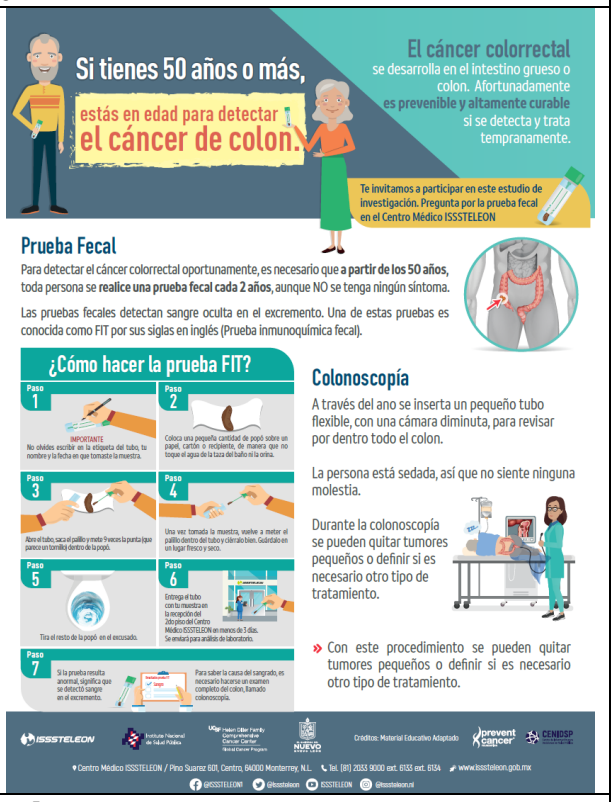
	Group					
Characteristics	Not able to contact* (n=58)	Excluded** (n=25)	Declined (n=64)	Lost to follow up*** (n=72)	Received and returned FIT (n=80)	**Overall (n=299)**
Age, (SD)	60.5 (7.7)	62.3 (8.1)	62.4 (7.9)	57.9 (9.8)	59.6 (6.8)	60.1 (8.3)
Average healthcare interactions in the last year, (SD)	6.6 (7.4)	19.3 (16.1)	10.8 (12.8)	12.1 (12.1)	15.4 (13.1)	12.3 (12.6)
Average days since last appointment, (SD)	80 (81.9)	56.6 (61.8)	64.1 (77.3)	64.8 (78.4)	52.1 (63.5)	62.7 (73.3)

FIT: fecal immunochemical test.
*Invalid phone number, or not able to be contacted by the call center
**No longer employed in local government, or met at least one exclusion criteria
*** Did not return FIT; scheduled recruitment appointment and were no-shows; received navigation twice but did not schedule an appointment.

Table 2.4. Characteristics of 21 adaptations made to the intervention, by components proposed by the Framework for Reporting Adaptations and Modifications-Expanded (FRAME).

Elements reported	Adaptations (n=21)
When did the modification occur? n(%)	
Pre-implementation/planning	14 (67)
Implementation	7 (33)
What is modified? n(%)	
Content	8 (38)
Training and evaluation	1 (5)
Implementation and scale up activities	4 (19)
Context (Format)	9 (43)
Context (Setting)	8 (38)
Context (Personnel)	10 (48)
What is the nature of the content modification? n(%)	
Adding elements	7 (33)
Removing/skipping elements	3 (14)
Shortening/condensing (pacing/timing)	3 (14)
Substituting	4 (19)
Tailoring/tweaking/refining	4 (19)
What is the goal of the modification? n(%)	
Improve effectiveness/outcomes	2 (10)
Improve feasibility	6 (29)
Improve fit with recipients	1 (5)
Increase reach or engagement	7 (33)
Increase retention	2 (10)
Increase satisfaction	1 (5)
To address cultural factors	1 (5)
What is the rationale for modification? n(%)	
Organization/Setting	
Available resources (funds, staffing, technology, space)	12 (57)
Competing demands or mandates	1 (5)
Location/accessibility	4 (19)
Regulatory/compliance	3 (14)
Provider (Clinical Judgement)	2 (10)
Recipient	
Access to resources	4 (19)
Cognitive capacity	3 (14)
Who participates in the decision to modify? n(%)	
ISSSTELEON director	3 (14)
Health services director	17 (81)
Program manager	15 (71)
Researcher	15 (71)
Individual Practitioners	19 (90)
Who makes the ultimate decision to modify? n(%)	
Individual Practitioners	5 (24)
Researcher	2 (10)
Health services director	11 (52)
ISSSTELEON director	1 (5)
Program manager	2 (10)

Table S2.5. Original and adapted versions of educational materials that were modified.

ORIGINAL VERSION	ADAPTED VERSION
Poster	
	
Postcard	
	

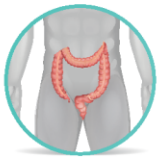
Brochure

¿Qué sabes del cáncer colorrectal?

Impacto en México

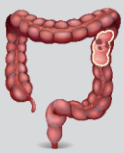
- Cuarto lugar de muertes por cáncer
- Primera causa de muerte por cáncer en la Ciudad de México

- El **colon** es la última sección del sistema digestivo.
- El colon también se conoce como intestino grueso.
- El recto es la parte final del colon.



Cáncer colorrectal

- Este cáncer puede presentarse en cualquier parte del colon.
- Comienza como un pólipo, que es un tumor benigno que se forma en el interior del colon.



- **El crecimiento de los pólipos es lento**, (de años) lo que permite tratarlos antes de que se conviertan en cáncer.

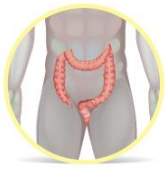
1

¿Qué sabes del cáncer colorrectal?

Impacto en México

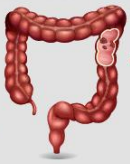
- Segundo lugar de muertes por cáncer en Nuevo León y a nivel nacional.

- El colon es la última sección del sistema digestivo.
- El colon también se conoce como intestino grueso.
- El recto es la parte final del colon.



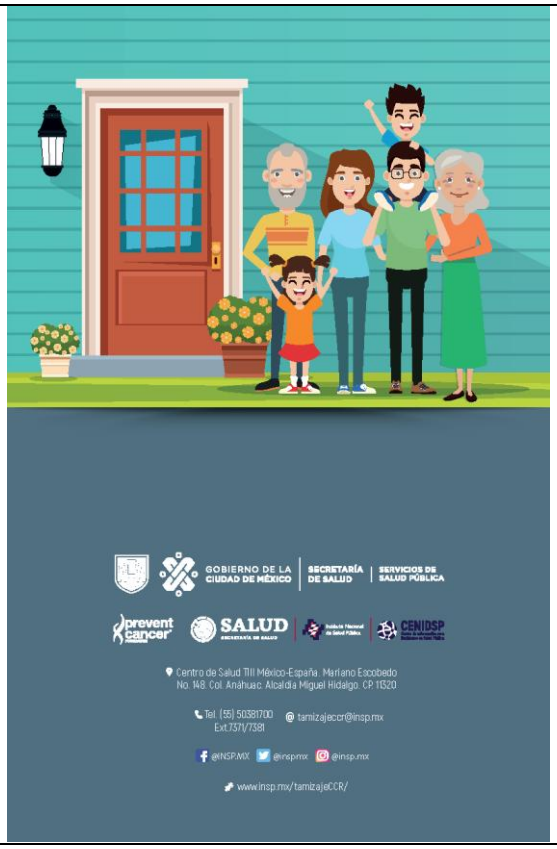
Cáncer colorrectal

- Este cáncer puede presentarse en cualquier parte del colon.
- Comienza como un pólipo, que es un tumor benigno que se forma en el interior del colon.



- **El crecimiento de los pólipos es lento**, (de años) lo que permite tratarlos antes de que se conviertan en cáncer.

1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CHAPTER 3. ZONE-LEVEL ASSOCIATION BETWEEN COLORECTAL CANCER SCREENING AND LATE-STAGE DISEASE AT DIAGNOSIS IN CALIFORNIA

Introduction

Despite the availability of effective screening strategies, colorectal cancer (CRC) remains a leading cause of cancer mortality, causing 904,000 deaths worldwide in 2022.[75,76] CRC is preventable through the detection and removal of precancerous polyps and is often curable when detected and treated at early stages.[77] Up until 2021, when the recommended age to start screening was lowered to 45, the U.S. Preventive Services Task Force recommended screening for all adults aged 50 to 75 years through either stool-based tests (highly sensitive fecal immunochemical test (FIT) every year, highly sensitive guaiac-based fecal occult blood test (gFOBT) every year or multi-targeted stool DNA test every 3 years) or visual exams of the colon and rectum (colonoscopy every 10 years, or CT colonography or flexible sigmoidoscopy every 5 years).[78] Colonoscopy is required to complete the screening process when any of the other recommended screening modalities is abnormal, as it provides a pathway for diagnosis and treatment through biopsy or removal of pathological lesions.

Effective screening approaches lead to the removal of polyps before they become cancers, and also cancer diagnosis at its earliest and, therefore, more treatable stages.[79,80] It is, therefore, expected that, over time, areas where a higher percentage of the population is up to date in their CRC screening, CRC will be diagnosed early and receive treatment before progressing to late-stage disease. However, it is possible areas with a high percentage of the population up to date with screening may still have a high proportion of late stage diagnoses due to barriers in getting through the process of diagnostic evaluation and treatment in a timely manner. There are many barriers to successful CRC screening, which threaten the completion of diagnosis and delivery of

appropriate treatments for patients with positive FIT results.[51,52,81] These include failures of the health care system to ensure completion of colonoscopy after non-invasive screening tests are found to be abnormal. Examples of such failures include failure of the health system to communicate test results to patients, failure to navigate them through the process of scheduling the procedure, long wait times in communities where endoscopy resources are limited, insurance problems that can lead to unexpected out-of-pocket costs, or patient factors such as inability schedule time off from work for the procedure, inability to arrange transportation to or from the procedure, or mistrust of the test results or of the health system itself.[81–83]

Therefore, it is relevant to study the association between the percentage of adults between the ages of 50 and 75 who had at least one type of CRC screening and the distribution of stage at diagnosis of colorectal cancer by geographic area. This will allow the identification of priority zones where screening efforts need to be increased, as well as areas where efforts to assess and address barriers to completing diagnostic work-up after a positive screening test need to be improved.

Methods

Study design and population

We conducted an ecological study, where our unit of analysis was census tract aggregation zones. These were developed by the California Health Maps team[84] with the goal of being able to examine cancer data at a smaller geography than county area levels to better inform cancer control, public health, and policy efforts. The census tract aggregation zones combine adjacent census tracts based on similarity in population sociodemographic characteristics including poverty, rurality, and racial and ethnic composition. There are a total of 578 zones in California, with population size varying from 51,229 to 98,764, while the number of census tracts in a zone range from 5 to 25.[84]

Given the COVID-19 pandemic impact on screening services usage starting in March 2020, we limited our analysis to years before 2020. Census-tract level estimates of up-to-date colorectal cancer screening were available starting in 2016, however they were limited to 500 cities across the country. Estimates for all census tracts in California, which allow for estimations at the zone level, were available for 2018 and every other year after. Since limiting our analyses to cases in 2018-2019 provided a small number of cancer cases for which: 1) 327 out of 578 zones had to be censored due to small counts, and 2) percentages were unstable, we expanded the years analyzed to colorectal cancer cases in the period 2015-2019 and under the assumption that screening during the period was relatively constant. Since the U.S. Preventive Services Task Force recommended screening for all adults aged 50 to 75 years during this period[78] the screening eligible population was defined as the population in this age group.

Up-to-date colorectal cancer screening

The Centers for Disease Control and Prevention's PLACES: Local Data for Better Health provides small-area estimates based on data from the Behavioral Risk Factor Surveillance System (BRFSS), American Community Survey estimates, and census population counts.[85,86] California Health Maps (University of California, San Francisco) obtains and publishes census tract aggregation zone estimates based on these census tract level estimates from PLACES.[84] Our primary exposure was then defined as the estimated percentages of the population 50-75 years who were up to date on colorectal cancer screening for each census tract aggregation zone in 2018. Up-to-date CRC screening was defined in the BRFSS as having one of the following: high-sensitivity fecal occult blood test (FOBT) in the past year; a colonoscopy within the past 10 years, or a sigmoidoscopy within the past 5 years.[87]

Colorectal cancer cases

Information on colorectal cancer cases was obtained from the California Cancer Registry.[88] Reporting all cancer cases is required by law in California. Eligibility criteria for cases included: incident cases in the period 2015-2019, with first primary in-situ or invasive colon (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)[89] codes C18.0, C18.2-18.9) or rectal cancer (codes C19 and C20). 63,586 cases met our inclusion criteria. Exclusion criteria included malignant neoplasm of appendix (C18.1) and Intestinal tract NOS (not otherwise specified) (C26.0) (n=2,556), aged <50 or >75 years at the time of diagnosis (n=22,944), reported by death certificate or autopsy only (n=297), not microscopically confirmed (n=515), not adenocarcinoma (n=3346), uncertain residential address or non-geocodable (n=1927), and not a California resident at the time of diagnosis (n=37). Following these exclusions, there was a total of 31,964 cases selected for analysis. Since any case counts lower than 11 are censored to ensure confidentiality, per California Cancer Registry policy, 4 census tract aggregation zones (0.6%) were excluded from the analysis, leaving 574 census tract aggregation zones available for analyses, which represented a total of 31,865 cancer cases.

Late stage at diagnosis was defined as having a Surveillance, Epidemiology, and End Results (SEER) summary stage of 3 or greater (regional lymph nodes involved or more).[90] Our primary outcome was the proportion of cases diagnosed in late stage in each census tract aggregation zone, calculated as the number of cases diagnosed in late stage divided by the total cancer cases diagnosed.

Covariates

Relevant covariates to include in our multivariable analyses were selected after displaying our hypothesized relationships in a directed acyclic graph and selecting the minimal sufficient adjustment set (MSAs) (**Figure 3.1**).[91] MSAs included percentage aged 50-74, percentage male, percentage of race and ethnicity, percentage uninsured, percentage with less than high school education, percentage with limited English proficiency, zone's index of concentration at the extremes (ICE) for income, and zone's socioeconomic status (SES).

Socioeconomic status (SES), racial and ethnic composition and uninsured at the census tract aggregation zone level for 2015-2019 were obtained from California Health Maps, University of California, San Francisco.[84] Information on the distribution of sex, age, limited English proficiency, less than high school education, and income (to estimate the index of concentration at the extremes for income) were obtained from the U.S. Census Bureau, 2015-2019 American Community Survey 5-Year Estimates at the census tract level and were estimated at census tract aggregation zones using a census tract-zones crosswalk.[92]

Socioeconomic status (SES) at the census tract aggregation zone level is a composite measure of seven indicator variables created by principal component analysis. This index was developed by the California Neighborhoods Data System and it is composed of census tract-level data from seven factors that influence socioeconomic status. These include education level (percent of people ages 25 and older with college, high school, and less than high school); percent of people with a blue-collar job; percent of people older than age 16 in the workforce, but without a job; median household income; percent of people below 200% of the federal poverty level; median rent and median house value.[93] Quintiles are based on state distribution, with quintile 1 being the lowest SES and 5 being the highest.

To account for the zone-level distribution of race and ethnicity, we used four variables for the percentage of the population that was: Non-Hispanic Asian American and Pacific Islander (AAPI), Non-Hispanic Black, Non-Hispanic White, and Hispanic or Latino. To adjust for the zone-level proportion of the population eligible for screening, and since population estimates at the census tract level are available by five-year age groups, we estimated and used the proportion of the population aged 50-74 for our analyses. Limited English proficiency (LEP) was defined as the percentage of the zone population that speaks a language other than English and speaks English less than "very well".

The ICE measures how the population in an area is concentrated given characteristics that are of advantage and disadvantage.[92] In contrast to SES, which is a composite measure that reflects the overall social and economic status of the area, ICE measures polarization within the area. ICE for income was calculated as: (households in the top quintile of US distribution of income (80^{th} percentile) – households in the bottom quintile of US distribution of income (20^{th} percentile))/total households with known income.[94,95] ICE for income ranges from -1 to 1. When all the population is disadvantaged (households in the bottom quintile of income), ICE equals -1. When all the population is advantaged (households in the top quintile of income), ICE equals +1. Information on household income by census tract was obtained from the U.S. Census Bureau, 2015-2019 American Community Survey 5-Year Estimates.[92] Income limits for quintiles for 2015-2019 were obtained from the U.S. Census Bureau Historical Income Tables for Households.[96] Following standard approaches, we then computed quintiles based on state distribution, with quintile 1 being the lowest ICE for income and 5 being the highest.[94,95]

To understand the joint distribution of screening and late-stage by county in California, we cross-classified the zones according to the tertiles of these two variables. CRC screening low tertile

ranged from 47.8% to 62.8%, medium tertile from 62.9% to 68.3%, and high tertile from 68.4% to 77.7%. CRC late-stage percentage low tertile ranged from 27.3% to 41.4%, medium tertile from 41.4% to 47.9%, and high tertile from 48.0% to 66.7%. These nine categories are presented graphically in a map, and as their distribution by county.

Statistical analysis

Descriptive statistics of census tract aggregation zones were calculated by colorectal cancer screening tertiles. Since we assume the relationship between the census tract aggregation zone proportion of up-to-date screening and the proportion of CRC cases diagnosed at a late stage, along with covariates, is linear, we conducted multivariable linear regression analyses. Based on diagnostic tests and visual inspections of residual plots, our data met assumptions for this type of analysis including residuals being normally distributed and homoscedasticity. The percentage with up-to-date screening was scaled for each unit to represent a 5% increase in screening.

The baseline model adjusted for the proportion aged 50-74 and the proportion of male population. Model 2 additionally adjusted for the percentage of non-Hispanic AAPI, Non-Hispanic Black, Hispanic, less than high school education, uninsured, and limited English proficiency. Given the high correlation between percentage non-Hispanic White and Hispanic (-0.79) and ICE for income and SES (0.91), Non-Hispanic White and SES were omitted from Model 2. In Model 3 we additionally adjusted for ICE for income. Given the high correlation between our exposure of interest (CRC screening) and ICE for income (0.81), we wanted to analyze the individual effect of adjusting for this covariate on our association of interest. We then conducted stratified analyses, using Model 2, by quintiles of ICE for income to account for potential confounding by ICE, and by the distribution of Hispanic population (< and > 50%) to observe the estimated association in areas with high and low proportions of this population.

Since our main models relied on the assumption of CRC screening being constant during the period, to assess the effect of different up-to-date screening percentages across the period, we conducted sensitivity analyses including screening estimates from both 2016 (only other available year with estimates at the census tract level) and 2018. Since CRC screening estimates for 2016 were only available for 66.3% (5,338/8,057) census tracts, we conducted the sensitivity analysis using the 2016 and 2018 average CRC screening in zones in which all census tract screening estimates were available for both years (n=170), and the 2018 screening estimates for the rest of the zones (n=404). Additionally, we found no statistically significant difference in screening for 2016 and 2018 in the 170 zones with estimates available for both years (t-test difference: 0.77%, 95%CI: -0.76, 2.30, p=0.320).

To determine statistical significance in our models, we used a two-sided $p<0.05$. Regression estimates and confidence intervals are described in the format: (estimate; 95% confidence interval [CI]). All statistical analyses were performed using Stata (Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Maps displaying the distribution by census tract aggregation zones of colorectal cancer screening, percent diagnosed at late-stage, and the categories product of the tertiles of these two variables were developed using R Statistical Software (v4.4.0; R Core Team 2024) and packages *biscale*, *bivariatechoropleths*, *dplyr*, *ggplot2*, *ggthemes*, *leaflet* and *sf*.[97–105] Census tract aggregation zone shapefiles were developed by the DREAM Lab (Disparities Research: Environment And oMics) at UCSF.[106] Since the data used in this analysis is publicly available, no IRB approval was required.

Results

The mean percentage of population (SD) aged 50-74 across the 574 zones was 26.6% (4.9), with a mean (SD) percentage of the population having received colorectal cancer screening of 65.0%

(6.2%). Regarding zone-level characteristics, a higher percentage of population aged 50-74, who identified as Non-Hispanic AAPI or as Non-Hispanic White, and higher ICE for income (higher very wealthy population proportion) were more frequent in zones in the highest tertile of CRC screening. In contrast, higher percentage of population who did not have health insurance, were born outside the United States, had less than High School education, had limited English proficiency, identified as Hispanic or Non-Hispanic Black were more frequent in zones in the lowest tertile of CRC screening. Specific characteristics of zones by tertiles of CRC screening are shown in **Table 3.1**.

Regarding the distribution of colorectal cancer screening across California (**Figure 3.2**), the zones with the lowest percentages were observed in Fresno, Los Angeles, San Bernardino, Riverside, and Kern counties, while the zones with the highest percent up to date on screening were observed in Orange, Contra Costa, Sonoma, San Mateo, and Santa Clara counties. The zones with the highest percentages of late-stage colorectal cancer were observed in San Bernardino, San Diego, Monterey, Fresno, and San Francisco counties, while the zones with the lowest were observed in San Bernardino, San Franciso, Sonoma, Contra Costa, and Tulare counties (**Figure 3.3**).

Counties that had the highest proportion of their zones in the high-screening tertile and low late-stage CRC tertile include Sonoma, Contra Costa, Santa Clara, and San Mateo. Counties that had the highest proportion of their zones in the low-screening tertile and high late-stage CRC tertile include Imperial, Fresno, Kings, and Kern. Additionally, counties that had the highest proportion of their zones in the high-screening tertile and high late-stage CRC tertile include Placer, Sonoma, San Francisco, and Santa Cruz (**Figure 3.4**). Los Angeles County had the highest number of zones in this category (n=11), but it represented 7% of its total number of zones. The highest proportion

of zones in Los Angeles were in the category of low-screening tertile and low late-stage CRC tertile (16.1%, n=25). Detailed distribution of zones across tertiles of screening and late-stage CRC by county are shown in **Table 3.2** and **Supplemental Table S3.3**.

After adjusting for zone-level distribution of age, sex, race, ethnicity, less than high school education, uninsured, and limited English proficiency there was 2.02% lower (95%CI -3.52, -0.51) percent late-stage at diagnosis for each 5% increase in CRC screening (Model 2). After adjusting for ICE for income quintiles (Model 3), the association between screening and the percentage of late-stage disease was no longer statistically significant (-0.94; 95%CI: -2.70, 0.83, p=0.297), likely driven by the high Pearson correlation between our exposure of interest and ICE for income (**Figure 3.5**).

In stratified analyses by ICE for income, we found that in zones in the lowest quintile (higher proportion of income-disadvantaged population), there was a 5.07 lower (95%CI: -9-72, -0.43) percentage of late-stage CRC for each 5% increase in screening. In contrast, in the highest quintile (higher proportion of income-advantaged population), the association observed was an additional 2.40% higher (95%CI: -1.98, 6.77) late-stage CRC for the same increase in screening, although not statistically significant (p=0.280). Of note, there seemed to be a trend of decreasing association of screening with a lower proportion of late-stage CRC as quintiles of ICE for income increased (**Figure 3.6**).

In models restricted to zones with more than half the population being Hispanic, we found a 4.38% lower (95%CI: -7.67, -1.08) percentage of late-stage CRC for each 5% increase in screening. In contrast, there was no association between the percent up-to-date on screening and the percent diagnosed at late stage in zones where less than half of the population were Hispanic (-0.43; 95%CI: -2.23, 1.37, p=0.637) (**Figure 3.7**). Notably, in this stratum, 31.20% of the zones

were in the high screening and medium or high late-stage CRC tertiles. Conversely, in areas with more than half of the population being Hispanic, there were no zones in this category. Sensitivity analyses which included estimates from 2016 (**Supplemental Table S3.4**) in 170 zones, were consistent with all our main model findings.

Discussion

In this ecological study in California, we observed an association between colorectal cancer screening and the proportion of late-stage colorectal cancer cases at the census tract aggregation zone level. For each additional five percent of the population that was up-to-date on screening, the percentage of colorectal cases diagnosed at late stage in that area decreased by 2.02%. Interestingly, this association appeared to be higher in less advantaged areas, including zones with a higher percentage of the population identified as Hispanic or Latino and in the lowest quintile of ICE for income. Finally, we identified counties in which efforts to increase screening are needed (such as Imperial, Fresno, Kings, and Kern counties) and counties with zones in which, although screening was high, there was still a high proportion of late-stage CRC at diagnosis, and therefore where further efforts to understand what could be driving these results are needed (such as Placer, Sonoma, San Francisco, and Santa Cruz counties).

Our main model results are consistent with studies at the individual level showing that colorectal cancer screening is associated with reduced stage at diagnosis and mortality.[79,80,107–110] In population-based studies analyzing changes in stage distribution with respect to colorectal cancer screening implementation, an increase in the proportion of early-stage CRC was found in countries that started implementing FIT-based screening and in which high colorectal cancer screening uptake and coverage were rapidly achieved.[111] In an organized colorectal cancer screening program in California for an insured population, in which screening transitioned from

being performed by physician request to direct-to-patient annual FIT outreach for all populations aged 51-75, a 36.2% decrease in advanced CRC incident rates was observed between 2000 and 2015.[112]

Our results from stratified analyses, specifically in areas with higher proportions of disadvantaged populations (more than half of the population being Hispanic and lower quintiles of ICE for income) tended to be consistent with this evidence, in which screening was associated with lower late-stage CRC at diagnosis. In contrast, in areas with a higher proportion of advantaged population (less than half of the population being Hispanic, and higher quintiles of ICE for income), there was no association.

There is evidence that barriers to receiving screening and completing diagnosis disproportionately affect disadvantaged groups. Documented barriers to the successful implementation of CRC screening that threaten the completion of diagnosis and delivery of appropriate treatments for patients with positive FIT results [51,52,81] include the cost of colonoscopy, procedure not being covered by health insurance, difficulties scheduling and attending appointments, existing health conditions as a competing priority, and distrust in the screening results and medical system.[82,83,113] Across the United States (US), prevalence of meeting CRC screening guidelines have been shown to be lower among Hispanic women compared to non-Hispanic White women, women in the lowest income level compared to the highest income level, and women with no form of health insurance compared to the ones that did.[114] Additionally, after controlling for differences in risk factors, Black individuals are no more likely than non-Hispanic White people to develop adenomas or CRC but are less likely to receive timely follow-up of a positive screening test or high-quality colonoscopy.[115] A study using electronic health records from community health centers across the US found that Hispanics had higher odds of going through

colorectal cancer screening and stool-based testing compared to non-Hispanic Whites, but they had lower odds of ever having a referral for an endoscopic study in general and even with a positive stool-based test compared to non-Hispanic Whites.[116] Finally, in a colorectal cancer screening program in federally qualified health centers, the most common barriers to timely colonoscopy documented in health records included lack of referral to a gastrointestinal specialist after an abnormal stool test and no valid insurance authorization.[117]

Given our results, we believe that in strata where less than half of the population are Hispanic or strata in higher quintiles of ICE for income, the high proportion of advantaged population may be able to consistently receive and complete screening and diagnosis processes, substantially contributing to a high area up-to-date screening. Conversely, disadvantaged populations in the same areas may not be able to either undergo any type of screening or, if they are able to start (e.g., go through stool-based testing and therefore contribute to higher screening), they might not be able to complete the diagnostic process (e.g., colonoscopy). Both circumstances would, therefore, contribute to an increase in the late-stage diagnosis proportion in the same area with high screening. This potential explanation would be consistent with our observation of a higher percentage of areas with high screening and medium or high late-stage CRC screening in these strata.

Mapping these areas can help prioritize and inform cancer interventions in these settings, in which different and context-specific approaches might be needed.[118,119] For example, areas could recognize the need to invest in screening and treatment for disadvantaged groups that have poor access to care and poor health outcomes. The San Francisco Cancer Initiative has already started following this approach by acknowledging the pockets of persistent poverty in the area and the importance of social determinants in leading to health inequities. They have taken a multi-level

transdisciplinary approach to improve prevention activities and cancer healthcare with active engagement with the community and local leadership, leading to quality improvement initiatives and novel approaches to navigating patients in safety-net settings.[120–123]

Our study allowed the identification and understanding of the distribution of areas by screening and late-stage CRC characteristics across counties in California. Furthermore, our stratified analysis results showed that relying primarily on CRC screening metrics to assess screening coverage might hide underlying health disparities, and reflect the need to further study, understand, and address barriers and disparities across areas. Our study is innovative since we use census tract aggregation zones as our unit of analysis. These units, smaller than counties but larger than census tracts, were developed to be used by organizations and policymakers to better understand disease burden and facilitate public health and policy planning. This allowed us to identify areas that can be prioritized depending on their screening and stage at diagnosis characteristics.[84] Additionally, we used the ICE for income, which characterizes the proportion of advantaged and disadvantaged populations based on income, to stratify our analyses.[124]

Limitations of our study include its ecological cross-sectional design. Our results at the zone level cannot be used to make inferences at the individual level, and since exposure and outcome were measured at one time, they cannot derive causal relationships. Additionally, since CRC screening measurements were available for 2018, our analyses assume that up-to-date screening was constant across zones during the analysis period (2015-2019). However, our sensitivity analyses, including available estimates for 2016, showed consistent results. Additionally, since individual-level information is not available, it is not possible to confirm whether the late-stage cases are mainly among disadvantaged populations in areas with higher ICE for income. There are also inherent limitations in measurements and estimations at the census tract

and zone level that are described in detail elsewhere, such as the use of the 2010 U.S. census as the post-stratification dataset for estimates as the census tract level, and possible recall or social desirability biases in self-reported surveys such as the BRFSS.[84,85,87,88,92,125,126]

Future analyses could be conducted at the individual level to better estimate the impact of screening on late-stage CRC accounting for neighborhood characteristics including social and built environment factors. Detailed data on colonoscopy completion, time to colonoscopy, and barriers to colonoscopy could help understand the disparities and impact of delay in completion of the diagnostic process on stage at diagnosis. These analyses would be useful to identify barriers and tailor strategies to address them and improve screening and early diagnosis in communities across California. Additionally, similar analyses could be conducted for other cancers to understand their screening and late-stage patterns and help prioritize and inform cancer interventions across areas.

Conclusion

Our study identified zones in California with low screening and high late-stage CRC, as well as regions with high late-stage CRC despite high screening. These data are needed to inform future cancer screening and treatment programs and help prioritize areas and tailor interventions. We found an overall association between screening and a lower proportion of late-stage disease by area. However, there was variation across California, highlighting the need for further study to understand and address the burden of colorectal cancer.

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Table 3.1. Characteristics of census tract aggregation zones by tertiles of the proportion of residents who are up-to-date for CRC screening (2015-2019).

	UNIT: Census tract aggregation zones Tertiles: percent of adults aged 50-75 years who have received CRC screening							
	Q1 (n=189)		**Q2 (n=195)**		**Q3 (n=190)**		**Total (n=574)**	
Percent of adults aged 50-75 years who have received CRC screening *[median (IQR)]*	58.2	(5.5)	65.7	(2.8)	71.2	(3.2)	65.7	(9.1)
Percentage of population aged 50-74	22.7	(3.1)	27.3	(3.7)	29.9	(4.8)	26.6	(4.9)
Percentage who are male	48.6	(2.8)	47.9	(2.1)	48.3	(2.2)	48.2	(2.4)
Statewide SES quintiles* *[n (%)]*								
1	105	(55.6)	7	(3.6)	0	(0.0)	112	(19.5)
2	66	(34.9)	47	(24.1)	3	(1.6)	116	(20.2)
3	17	(9.0)	81	(41.5)	17	(8.9)	115	(20.0)
4	1	(0.5)	51	(26.2)	64	(33.7)	116	(20.2)
5	0	(0.0)	9	(4.6)	106	(55.8)	115	(20.0)
Index of Concentration at the Extremes for income** *[median (IQR)]*	-0.1	(0.2)	0.1	(0.2)	0.3	(0.2)	0.1	(0.3)
Percent of residents** *[mean (sd)]*								
Who did not have health insurance	11.4	(3.9)	6.8	(2.2)	4.3	(1.8)	7.5	(4.0)
Who were born outside the United States	32.9	(10.3)	25.3	(11.9)	22.7	(9.8)	26.9	(11.5)
Who had less than High School education	30.8	(9.3)	14.3	(4.7)	6.8	(3.2)	17.3	(11.8)
With Limited English Proficiency	27.6	(9.8)	15.9	(8.0)	10.2	(5.1)	17.9	(10.6)
Percentage of population identified as: § *[mean (sd)]*								
Hispanic	63.5	(16.2)	35.3	(13.5)	18.5	(8.4)	39.0	(22.7)
Non-Hispanic Asian/Pacific Islander	11.7	(12.6)	17.3	(15.7)	18.1	(12.8)	15.7	(14.0)
Non-Hispanic Black	7.3	(6.8)	7.2	(8.1)	4.3	(3.7)	6.3	(6.6)
Non-Hispanic White	17.1	(11.8)	39.6	(18.9)	58.6	(14.4)	38.5	(22.8)

Abbreviations: IQR interquartile range; SD standard deviation; SES: Socioeconomic status.
*Quintile 5=highest SES, Quintile 1=lowest SES
**Index of concentration at the extremes for income ranges from -1 to 1: when all the population is disadvantaged ICE=-1, when all population is advantaged ICE=1.
***Across all population at census tract level

Table 3.2. Census tract aggregation zones distribution (n) of colorectal cancer screening (only low and high tertile) and late-stage colorectal cancer tertiles by California counties, in counties with ten or more zones (n=15).

County	Low CRC screening (47.8 -62.8%)			High CRC screening (68.4-77.7%)			Total zones* (n=574)	Total CRC cases (2015-2019)
	Tertile of late-stage CRC			Tertile of late-stage CRC				
	Low (n=53)	Med. (n=71)	High (n=65)	Low (n=71)	Med. (n=58)	High (n=61)		
Fresno	0	2	7	0	0	2	13	630
Kern	0	2	5	1	0	0	11	504
San Bernardino	5	9	7	1	0	0	32	1,682
Los Angeles	25	24	21	16	13	11	155	8,356
San Diego	2	5	6	8	3	3	47	2,424
Riverside	6	5	4	0	1	0	33	2,028
San Francisco	0	1	1	2	1	5	13	715
Ventura	1	2	1	2	0	1	13	622
Contra Costa	0	1	1	6	2	4	17	1,003
Santa Clara	0	2	1	8	5	5	27	1,574
Alameda	0	1	1	5	3	1	23	1,305
Orange	7	4	0	7	13	8	49	2,474
Sacramento	1	2	0	4	5	5	23	1,341
San Mateo	0	0	0	3	2	2	12	595
San Joaquin	0	3	0	0	0	0	11	646

Late-stage colorectal cancer tertiles: Low 27.3-41.4; Medium (Med.) 41.4-47.9; High 48.0-66.7.
*Total zones in the County also include zones in the Medium Tertile of colorectal cancer screening, in addition to the zones shown in the table on the low and high colorectal screening tertiles.
Color indicates the percentage these zones in the cell represent out of the total zones in their County:

Counties are sorted by high to low percentage of zones in Low CRC screening - High Late Stage category

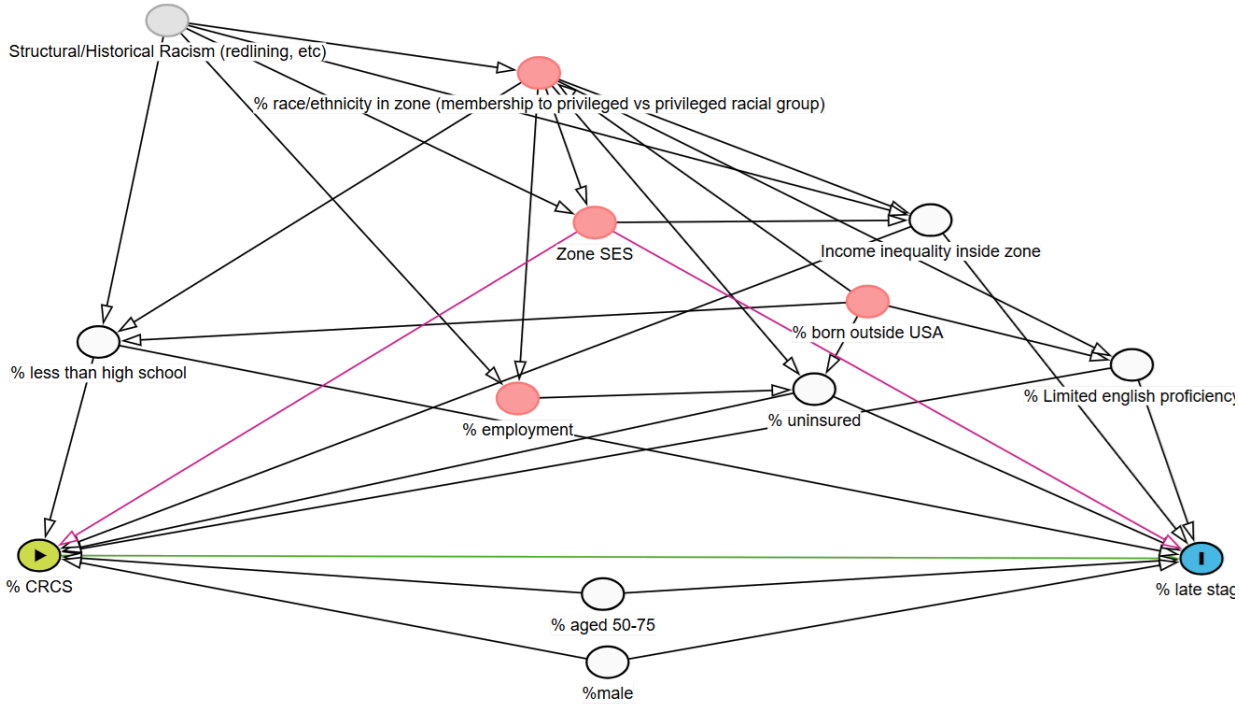

Figure 3.1. Directed acyclic graph of hypothesized relationships between relevant covariates to include in multivariable analyses.

SES: Socioeconomic status. Income inequality inside zones measured as index of concentration at the extremes for income. Variables adjusted for in the models are shown as white circles.[91] Given the high correlation between the index of concentration at the extremes for income and SES (0.91), SES was omitted from the fully adjusted model.

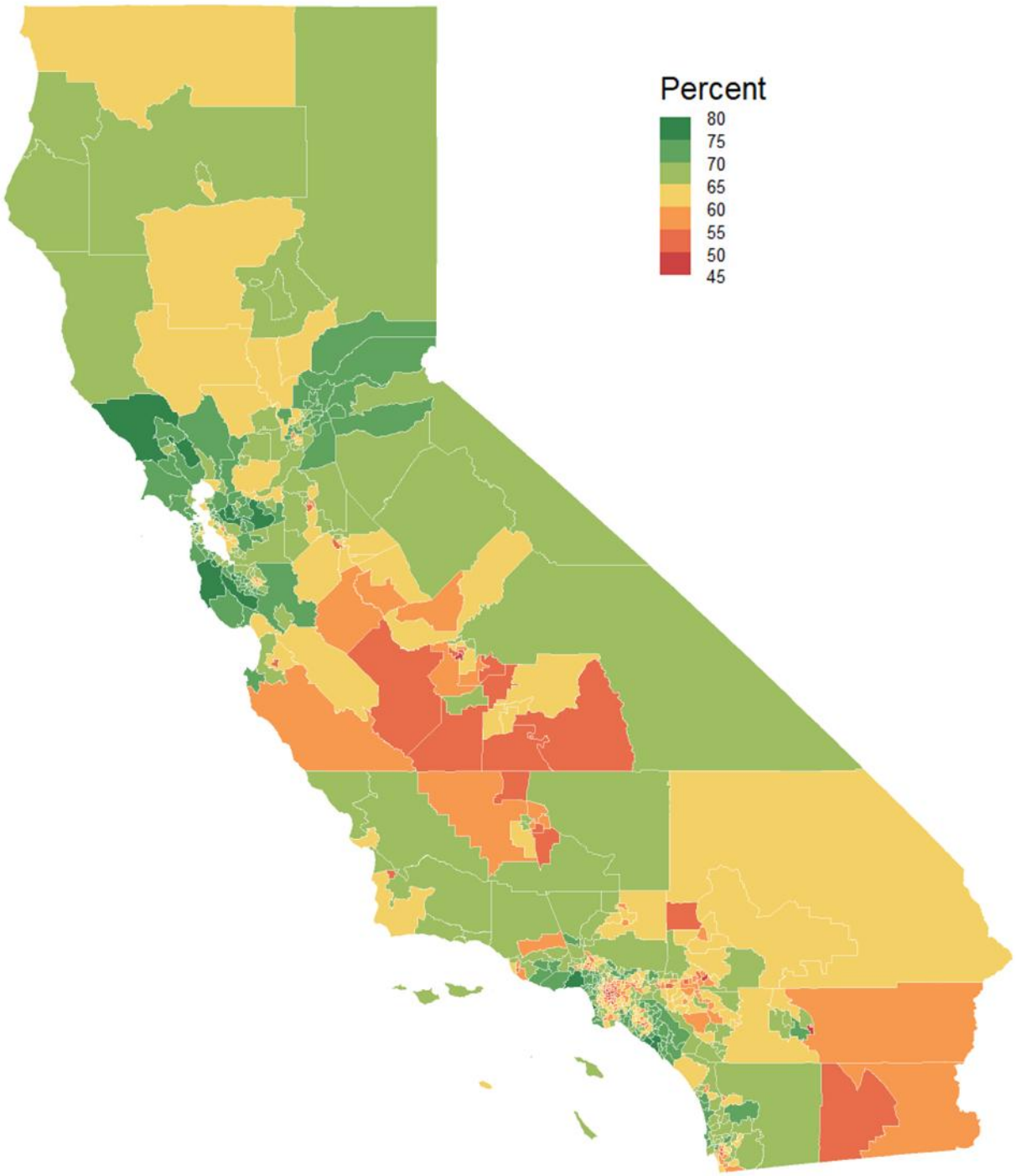

Figure 3.2. Percent of up-to-date colorectal cancer screening at census tract aggregation zone level (California Health Maps, 2018).

Zones shown in dark gray (n=4) were excluded from analyses to ensure confidentiality, per California Cancer Registry policy.

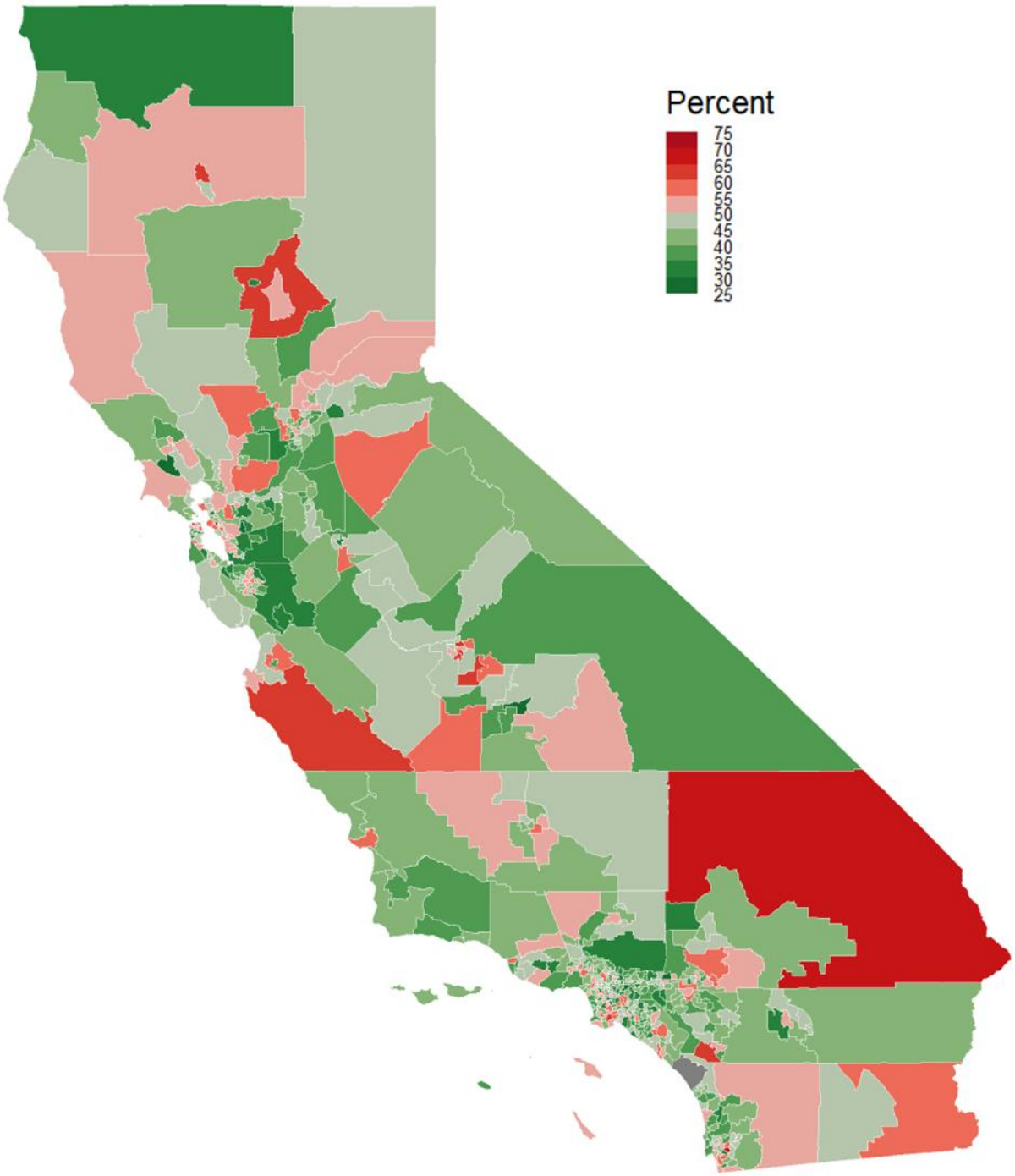

Figure 3.3. Percent of colorectal cancer cases diagnosed at late stage at census tract aggregation zone level (California Cancer Registry, 2015-2019).

Zones shown in dark gray (n=4) were excluded from analyses to ensure confidentiality, per California Cancer Registry policy.

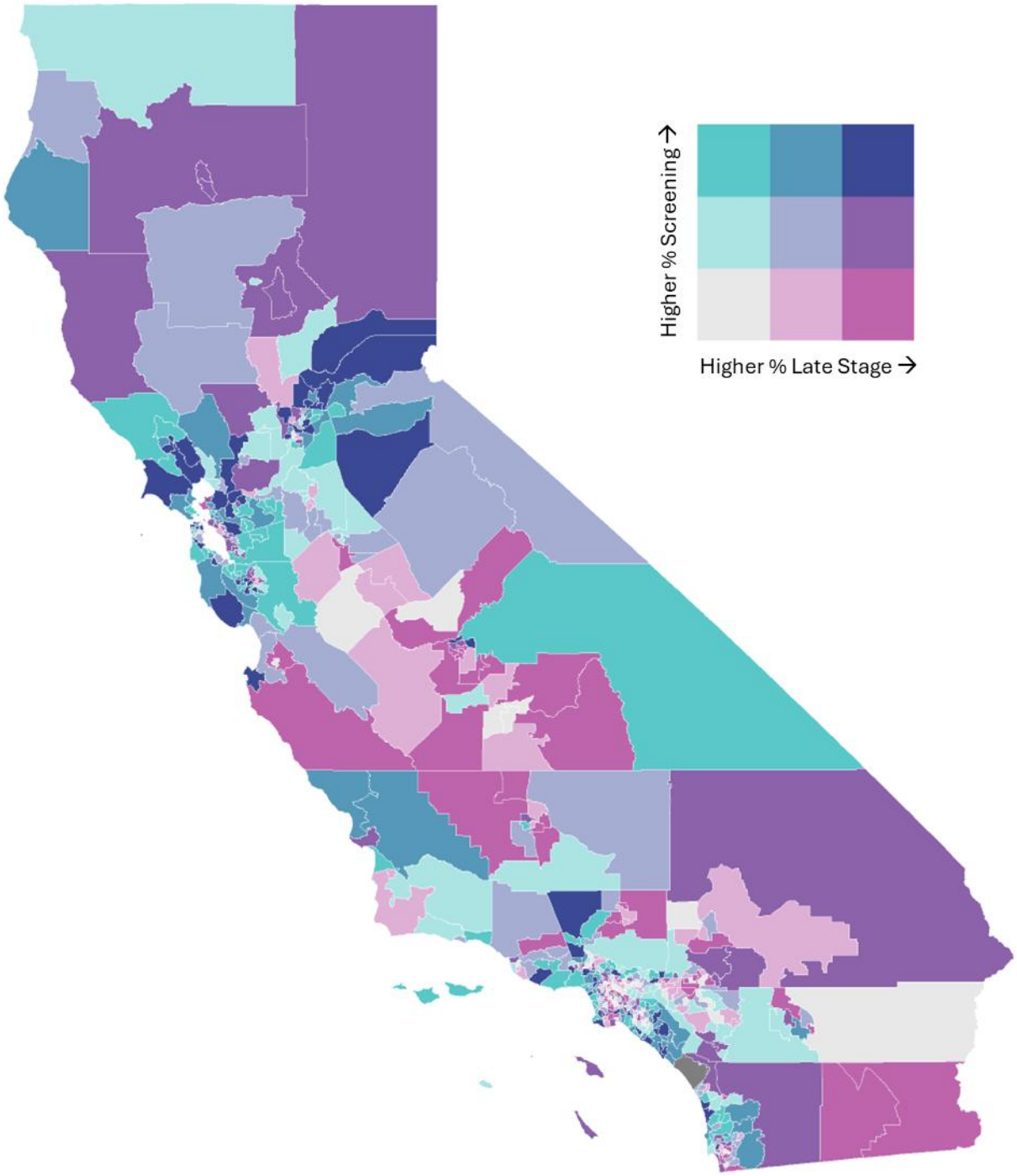

Figure 3.4. Percent of colorectal cancer cases diagnosed at late stage and up-to-date colorectal cancer screening tertiles at census tract aggregation zone level (California Cancer Registry and California Health Maps, 2018).

Zones shown in dark gray (n=4) were excluded from analyses to ensure confidentiality, per California Cancer Registry policy.

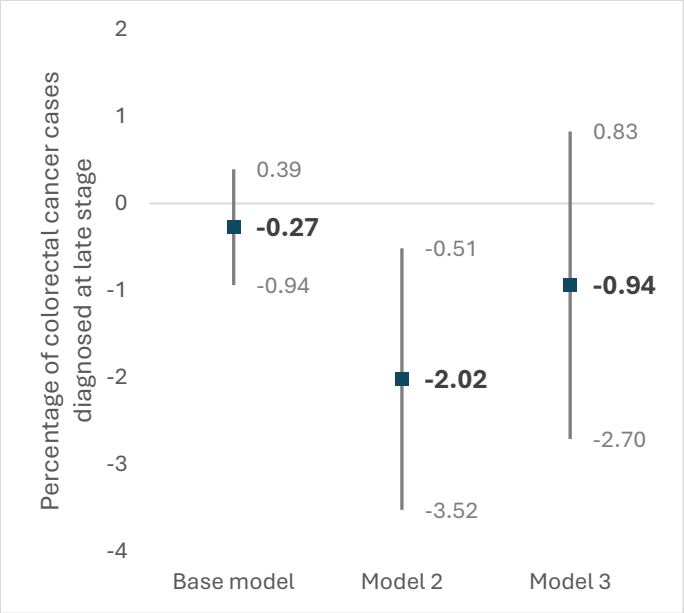

Figure 3.5. Association between colorectal cancer screening and percentage of colorectal cancer cases diagnosed at late stage by census tract aggregation zone in California 2015-2019 (n=574).

Association shown for a 5% increase in colorectal cancer screening. Base model adjusted for percentage aged 50-74 and percentage male. Model 2 was additionally adjusted for non-Hispanic AAPI, Non-Hispanic Black, Hispanic, less than high school education, uninsured, and limited English proficiency. Model 3 additionally adjusted for ICE for income.

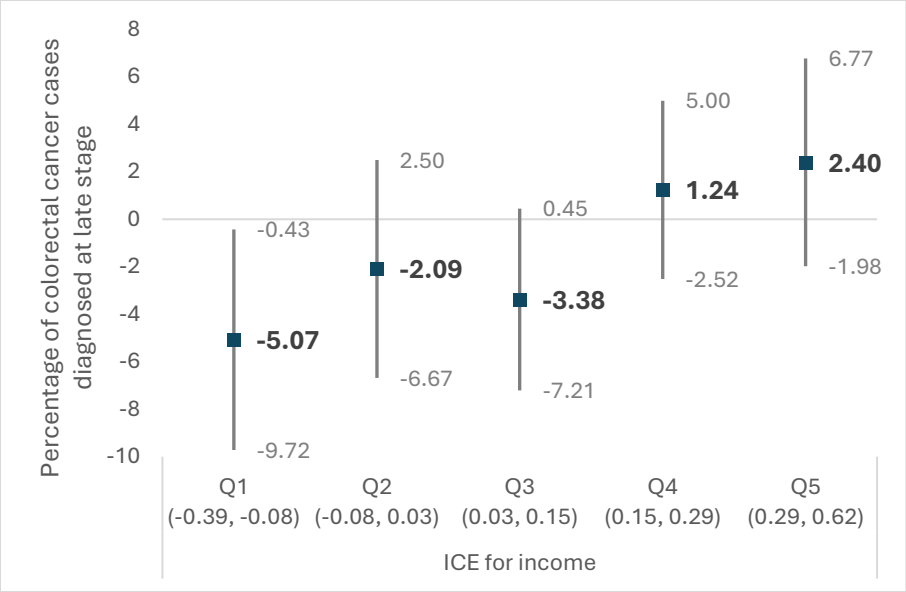

Figure 3.6. Association between colorectal cancer screening and percentage of colorectal cancer cases diagnosed at late stage by census tract aggregation zone in California (n=574), stratified by quartiles of Index of Concentration at the Extremes for income.

Association shown for a 5% increase in CRC screening in zone. Q: Quintile; ICE: Index of concentration at the extremes. ICE for income ranges from -1 to 1: when all the population is disadvantaged ICE=-1, when all population is advantaged ICE=1. Quintile 5=highest ICE for income, Quintile 1=lowest ICE for income. Models adjust for percentage aged 50-74 and percentage male, percentage non-Hispanic AAPI, Non-Hispanic Black, Hispanic, less than high school education, uninsured, and limited English proficiency.

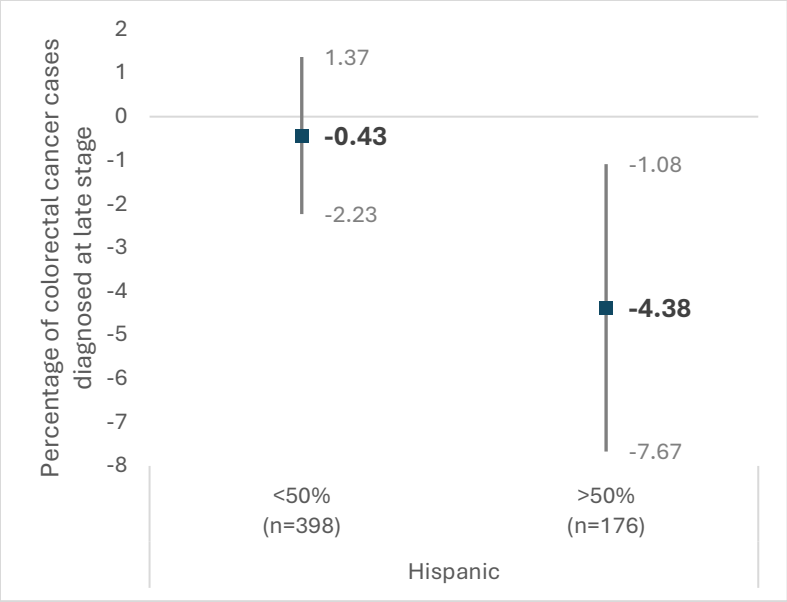

Figure 3.7. Association between colorectal cancer screening and percentage of colorectal cancer cases diagnosed at late stage by census tract aggregation zone in California 2015-2019 (n=574), stratified proportion of Hispanic population.

Association shown for a 5% increase in CRC screening in zone. Models adjust for percentage aged 50-74 and percentage male, percentage non-Hispanic AAPI, Non-Hispanic Black, Hispanic, less than high school education, uninsured, and limited English proficiency.

Table S3.3. Census tract aggregation zones distribution of colorectal cancer screening and late-stage colorectal cancer by California counties.

Counties	**Low CRC screening** (47.8 -62.8%)			**Medium CRC screening** (62.9-68.3%)			**High CRC screening** (68.4-77.7%)			**Total zones* (n=574)**	**Total CRC cases (2015-2019)**
	Tertile of late stage CRC			Tertile of late stage CRC			Tertile of late stage CRC				
	Low (n=53)	Med. (n=71)	High (n=65)	Low (n=68)	Med. (n=65)	High (n=62)	Low (n=71)	Med. (n=58)	High (n=61)		
Los Angeles	25	24	21	20	12	13	16	13	11	155	8,356
Orange	7	4	0	4	3	3	7	13	8	49	2,474
San Diego	2	5	6	4	10	6	8	3	3	47	2,424
Riverside	6	5	4	9	4	4	0	1	0	33	2,028
San Bernardino	5	9	7	2	3	5	1	0	0	32	1,682
Santa Clara	0	2	1	3	0	3	8	5	5	27	1,574
Alameda	0	1	1	1	2	9	5	3	1	23	1,305
Sacramento	1	2	0	2	2	2	4	5	5	23	1,341
Contra Costa	0	1	1	0	1	2	6	2	4	17	1,003
Fresno	0	2	7	0	0	2	0	0	2	13	630
San Francisco	0	1	1	2	1	0	2	1	5	13	715
Ventura	1	2	1	1	4	1	2	0	1	13	622
San Mateo	0	0	0	1	3	1	3	2	2	12	595
Kern	0	2	5	1	1	1	1	0	0	11	504
San Joaquin	0	3	0	5	3	0	0	0	0	11	646
Stanislaus	0	1	2	2	3	0	0	0	0	8	463
Sonoma	0	0	0	0	0	0	3	1	3	7	430
Tulare	3	2	2	0	0	0	0	0	0	7	310
Placer	0	0	0	0	0	0	0	1	5	6	338
Santa Barbara	0	2	0	2	1	0	1	0	0	6	350
Solano	0	0	0	2	2	1	0	0	1	6	409
Monterey	1	0	2	0	1	0	0	0	1	5	289
Marin	0	0	0	0	0	0	1	2	1	4	229
San Luis Obispo	0	0	0	0	0	1	1	2	0	4	243
Butte	0	0	0	1	0	2	0	0	0	3	214
Merced	1	2	0	0	0	0	0	0	0	3	228
Santa Cruz	0	0	0	0	1	0	0	1	1	3	233
Yolo	0	0	0	2	0	1	0	0	0	3	140
El Dorado	0	0	0	0	0	0	1	1	0	2	117
Humboldt	0	0	0	0	1	0	0	1	0	2	130
Imperial	0	0	2	0	0	0	0	0	0	2	149
Kings	0	0	1	1	0	0	0	0	0	2	92
Napa	0	0	0	1	0	0	0	1	0	2	123
Shasta	0	0	0	0	0	2	0	0	0	2	130
Amador, Calaveras	0	0	0	0	0	0	0	0	1	1	102
Fresno, Madera	0	0	1	0	0	0	0	0	0	1	55
Fresno, Tulare, Inyo	0	0	0	0	0	0	1	0	0	1	77
Glenn, Shasta, Tehama	0	0	0	0	1	0	0	0	0	1	97
Lake, Colusa	0	0	0	0	1	0	0	0	0	1	82
Madera	1	0	0	0	0	0	0	0	0	1	63
Mendocino	0	0	0	0	0	1	0	0	0	1	121
Nevada	0	0	0	0	0	0	0	0	1	1	91
San Benito	0	0	0	0	1	0	0	0	0	1	37

Counties	Low CRC screening (47.8 -62.8%)			Medium CRC screening (62.9-68.3%)			High CRC screening (68.4-77.7%)			Total zones* (n=574)	Total CRC cases (2015-2019)
	Tertile of late stage CRC			Tertile of late stage CRC			Tertile of late stage CRC				
	Low (n=53)	Med. (n=71)	High (n=65)	Low (n=68)	Med. (n=65)	High (n=62)	Low (n=71)	Med. (n=58)	High (n=61)		
Sierra, Modoc, Lassen, Plumas	0	0	0	0	0	1	0	0	0	1	55
Siskiyou, Del Norte	0	0	0	1	0	0	0	0	0	1	75
Siskiyou, Shasta, Trinity	0	0	0	0	0	1	0	0	0	1	76
Sutter	0	1	0	0	0	0	0	0	0	1	73
Tulare, Kern	0	0	0	0	1	0	0	0	0	1	65
Tuolumne, Mariposa	0	0	0	0	1	0	0	0	0	1	61
Tuolumne, Mono, El Dorado, Alpine	0	0	0	0	1	0	0	0	0	1	76
Ventura, Kern	0	0	0	0	1	0	0	0	0	1	76
Yuba	0	0	0	1	0	0	0	0	0	1	67

Late-stage colorectal cancer tertiles: Low 27.3-41.4; Medium (Med.) 41.4-47.9; High 48.0-66.7.
Census tract aggregation zones with census tracts in different counties are listed individually.

Table S3.4. Sensitivity analyses with different definitions of colorectal cancer screening using 2016 and 2018 census tract level estimates.

	Number of zones included	Model 2*	Model 3*	Model 2 + Stratified by Quintiles of ICE for income*				
				Q1** (-0.39, -0.08)	Q2** (-0.08, 0.03)	Q3** (0.03, 0.15)	Q4** (0.15, 0.29)	Q5** (0.29, 0.62)
-Subsample (n=170): zones in which all census tract screening estimates were available for both years **Screening Definition**: Average 2016-2018 CRC screening	**574**	-1.86 (-3.34, -0.38)	-0.81 (-2.56, 0.95)	-3.23 (-7.38, 0.92)	-3.18 (-8.03, 1.66)	-3.04 (-6.92, 0.84)	2.22 (-1.56, 6)	1.82 (-2.81, 6.44)
-Subsample (n=404): zones in which screening estimates were not available for 100% of the population at the census tract level for both years **Screening Definition**: 2018 CRC screening								

Association shown for a 5% increase in colorectal cancer screening. Model 2 adjusted for percentage aged 50-74, percentage male, non-Hispanic AAPI, Non-Hispanic Black, Hispanic, less than high school education, uninsured, and limited English proficiency. Model 3 additionally adjusted for ICE for income.

CT: Census tract. ICE: Index of concentration at the extremes for income. ICE ranges from -1 to 1: when all the population is disadvantaged ICE=-1, when all population is advantaged ICE=1.

* Estimates and (95% confidence intervals)

** Ranges of ICE of each quintile

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APPENDIX

Adaptations and selected evaluated components using the Framework for Reporting Adaptations and Modifications-Expanded.[63]

	Description of change		Who participates in the decision to modify?*					What is modified?				What is the nature of the content modification?	What is the goal of the modification?
	Component to be modified	Modification	Director	Health services director	Program manager	Researcher	Individual Practitioners	Content	Training and evaluation	Implementation and scale up	Context		
1	Educational materials/ outreach**	Postcard to be used in email for outreach instead of delivered at home		✓*	✓	✓	✓				✓	Substituting	Increase reach or engagement
2	Outreach**	Instead of door-to-door, automated phone call to remind them of the invitation		✓*	✓	✓	✓				✓	Substituting	Increase reach or engagement
3	Outreach**	Instead of door-to-door, navigation if they had not scheduled an appointment after automated phone call		✓*	✓	✓	✓				✓	Substituting	Increase reach or engagement
4	Educational materials (booklet, poster, video and postcard)**	Changed main phrase in educational materials, contact info and logos		✓	✓	✓*	✓	✓				Tailoring/ tweaking/ refining	To address cultural factors
5	Enrollment in screening**	Had to schedule an appointment with Primary Care Physician instead of being enrolled by promoters		✓*	✓	✓	✓				✓	Adding elements	Improve feasibility
6	Enrollment in screening**	Enrollment in at-work medical office (additional to Medical Center)		✓*	✓	✓	✓				✓	Adding elements	Improve fit with recipients
7	Information Collection /Monitoring**	Information would be collected in EHR. Own follow-up platform would be developed instead of using REDCAP and Tableau	✓*				✓			✓	✓	Substituting	Improve feasibility
8	FIT return**	Participants would receive a message reminding them to return their FIT through their Institutional app	✓				✓*	✓			✓	Adding elements	Improve effectiveness/ outcomes
9	FIT processing**	FITs would be shipped to Mexico City for processing. Results would be added to EHR		✓	✓	✓*					✓	Tailoring/ tweaking/ refining	Improve feasibility
10	FIT results**	Negative results would be received through the Institutional app and during their next primary care appointment	✓				✓*				✓	Tailoring/ tweaking/ refining	Improve feasibility

	Description of change		Who participates in the decision to modify?*					What is modified?				What is the nature of the content modification?	What is the goal of the modification?
	Component to be modified	Modification	Director	Health services director	Program manager	Researcher	Individual Practitioners	Content	Training and evaluation	Implementation and scale up	Context		
11	FIT results**	Participants with positive results would be contacted by the call center to schedule an appointment with the Gastroenterologist		✓*	✓	✓	✓				✓	Removing/ skipping elements	Increase retention
12	Preoperative assessment**	Participants with anesthetic or bleeding risk were referred for lab tests before their colonoscopy		✓			✓*	✓			✓	Adding elements	Improve feasibility
13	Preoperative assessment**	Reduction in studies requested for preoperative assessment		✓			✓*	✓			✓	Removing/ skipping elements	Increase retention
14	Staff training**	Staff training provided by the quality improvement department staff		✓*	✓	✓			✓			Tailoring/ tweaking/ refining	Improve feasibility
15	Outreach***	Emails that bounced would go directly to automated call.		✓	✓*	✓	✓			✓		Shortening/ condensing (pacing/ timing)	Increase reach or engagement
16	Outreach***	Increase the number of daily emails sent		✓	✓*	✓	✓			✓		Shortening/ condensing (pacing/ timing)	Increase reach or engagement
17	Outreach***	Navigation if they had not scheduled an appointment after email and automated call without waiting 14 days after call		✓*	✓	✓	✓			✓		Shortening/ condensing (pacing/ timing)	Increase reach or engagement
18	Outreach***	Second navigation call to patients who did not attend their recruitment appointment and who asked to be contacted at another time		✓*	✓	✓	✓	✓				Adding elements	Increase reach or engagement
19	Outreach***	No tracking of automated phone calls that were picked up					✓*	✓				Removing/ skipping elements	-
20	FIT return***	Participants who had not returned their FIT received a reminder through a call center phone call		✓*	✓	✓	✓	✓			✓	Adding elements	Improve effectiveness/ outcomes
21	FIT results***	Participants with negative FIT results received a call center phone call to let them know they were available		✓*	✓	✓	✓	✓			✓	Adding elements	Increase satisfaction

* The person who made the final decision to modify has been marked with '*'
** Modification was made pre-implementation and was proactive.
*** Modification was made during implementation and was reactive.

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