Helping Patients and Providers Make Better Decisions about Colorectal Cancer Screening

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Helping Patients and Providers Make Better Decisions about Colorectal Cancer Screening

Principal Investigator: Peter H. Schwartz, PhD, MD
Department of Medicine, Indiana University School of Medicine

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Measuring the Impact of Providing Personalized Risk Information to Patients and their Providers

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A. SPECIFIC AIMS: The colorectal cancer (CRC) screening rate in the U.S. remains under 65%,[1] significantly lower than for breast and cervical cancer (RQ-3).[2-4] This low rate means that thousands of people die of CRC unnecessarily. Precision CRC prevention – providing information about an individual's specific risk for CRC – has great promise to increase uptake and improve decision making. This approach, however, has not been widely tested or adopted.

Low uptake of CRC screening is due, in part, to providers' offering only colonoscopy, which many patients are reluctant to undergo. Studies show that uptake increases when patients are offered non-invasive options such as the fecal immunochemical test (FIT) or DNA/FIT test (Cologuard),[5] for which only some patients require a follow-up colonoscopy.[6] Fully considering all options requires knowing the comparative effectiveness of the tests, which depends, in part, on a person's current risk of advanced colorectal neoplasia (ACN), i.e. a CRC or advanced, precancerous polyp.[7-12] Colonoscopy has greater effectiveness in patients with a higher risk of ACN than in those with a lower risk, due to the higher likelihood of detecting and removing it.[7,13] As ACN risk gets smaller, the comparative effectiveness of colonoscopy decreases, and the attractiveness of non-invasive options increases. [7,13] Even among individuals with "average risk," i.e. without a family history or medical condition that confers high risk for CRC, the risk of ACN varies greatly, as much as 10-fold (22% vs. 2%).[7]

Our research team has developed and pilot tested a CRC screening decision aid and provider message that discloses the patient's current risk of ACN, based on a prediction rule that was developed and validated by Dr. Tom Imperiale, a member of our team.[7,8] The Imperiale rule has important advantages over others: it uses just five variables that are easy to collect and identifies a wide range of risk for current ACN among average risk patients. For patients with "high-average" risk (22%), personalized messages in our decision aid and provider notification highlight the advantage of colonoscopy because of the likelihood of finding and removing an ACN. For patients at low risk for ACN (2% or 4%), personalized messages highlight the advantage of stool testing, due to the relatively low chance of failing to detect ACN.

In our pilot testing, personalized messages including ACN risk increased patients' intent to be screened and influenced their test choice. Over 95% of patients (156 of 160) who viewed personalized information agreed that others considering screening should receive this information. Providers rated the personalized message as helpful in 93% of cases presented to them (26 of 28), and the personalized message changed their recommended test in 57% (16 of 28). Working with our partner health systems, we have piloted a system that holds promise for delivering decision aids to patients effectively and affordably in clinics, through the patient portal of electronic health record systems.

Study Aims: Our *long-term goal* is to increase uptake of CRC screening by informing and improving patient and provider discussion and decisions. The *main objective* of this application is to test whether providing patients and their providers with personalized messages about ACN risk results in higher screening uptake and higher decision quality (i.e., informed choice and receipt of the preferred screening test), compared to an approach that does not utilize ACN risk.

Aim 1: To measure the impact on patient decision quality and screening uptake of providing patients and their providers with personalized messages about the patient's current risk of having advanced colorectal neoplasia (ACN).

Primary hypotheses: The proportion of patients who make a **high-quality decision** and **complete screening** at six months will be higher

1.1 for patients who receive the personalized message than those who do not, and

1.2 for patients whose providers receive the personalized message than those whose providers do not.

Aim 2: To examine mediators and moderators of the interventions' effectiveness.

Study Design: To achieve these aims, we will conduct a 2x2 design, cluster randomized, controlled trial (see **Table 1**) to compare decision quality and screening uptake in four groups of patients who view a decision aid:

- Group 1) without the personalized message and whose providers do not receive the personalized message (control group),
- Group 2) with the personalized message and whose providers do not receive the personalized message,
- Group 3) without the personalized message and whose providers receive the personalized message, and
- Group 4) with the personalized message and whose providers receive the personalized message.

TABLE 1	Patient views:	
Provider receives:	Decision aid WITHOUT personalized message	Decision aid WITH personalized message
Screening reminder	Group 1	Group 2
Screening reminder + Personalized message	Group 3	Group 4

Our study is **innovative** since it employs a newly developed ACN prediction rule and informs patients and their providers about the implications of this risk level for test choice utilizing an electronic health record. Our study is **significant** since it will identify the impact of providing personalized information to providers and patients and will collect information

1.0 Background & Rationale

CRC Screening: Colorectal cancer (CRC) is the second-largest cancer killer in the U.S., and low screening rates leads to thousands of preventable deaths. Each year, over 140,000 people are diagnosed with CRC and more than 50,000 die.[2] Under 65% of eligible adults are current with screening, a rate that pales in comparison to breast and cervical cancer screening.[2-4] Raising the CRC screening rate to 80% by 2018, which was the Colorectal Cancer Roundtable's goal, would have prevented over 20,000 deaths from CRC per year and 203,000 deaths by 2030.[14]

"Precision prevention" in this area is a promising way to motivate screening and help patients choose the best test for them. Leading guidelines approve multiple testing strategies, including colonoscopy every 10 years, flexible sigmoidoscopy every five years, annual stool testing with high-sensitivity fecal occult blood testing (FOBT) or fecal immunochemical testing (FIT), or stool testing for high risk DNA.[4,6,15] Colonoscopy is the most sensitive and specific for identifying polyps or cancers,[15-17] and is best known. But it is an invasive procedure involving a lengthy preparation, IV sedation, and the need to take a day off. There are significant risks, including hemorrhage and perforation.[6]

Stool (or fecal) blood testing is the second most commonly utilized approach, and many patients prefer stool testing to colonoscopy when they are informed about both tests.[18-24] We concentrate here on FIT since it is widely used and available nationwide, and is recommended by all major guideline organizations.[4,6,15] Stool blood testing may be done in the privacy of one's home, is low cost, and requires no preparation. The main limitations are that it must be done annually, it requires the patient to handle stool, and all positive tests require evaluation with colonoscopy. Newer forms of stool testing, such as Cologuard, which combines FIT with testing for high risk DNA, are being used relatively rarely, and they can be considered similarly to FIT for this application, except that they may be performed every 3 years.[6]

Primary care providers often fail to describe alternatives to colonoscopy,[25-27] causing patients who are reluctant to undergo this test put off screening entirely, instead of choosing the less invasive stool test (RQ-3). In a recent study, an outreach program that recommended just colonoscopy for screening resulted in a 38% uptake, while recommending a stool test or offering a choice between colonoscopy and stool test resulted in uptake of 67% and 69%, respectively.[5] Multiple national organizations recommend that providers describe and explain the alternatives to colonoscopy. A slogan used by the 80 by 2018 initiative declares that "The best CRC screening test is the one that gets done."[28,29]

Precision prevention: Guidelines recommend only colonoscopy for patients with particularly high risk for CRC, such as those with a significant family history, a genetic condition such as Lynch syndrome, or inflammatory bowel disease.[4,30] Approximately 90% of patients lack these risk factors and are considered "average risk," so can choose any CRC screening test, according to guidelines. But even within this average risk group, people have varying chances of having an "advanced colorectal neoplasm" (ACN), i.e. a colorectal cancer or precancerous polyp.[7,8] A polyp counts as "advanced" if it is greater than 1 cm or has high-risk pathology, e.g. villous histology or high-grade dysplasia.

An individual's chance of currently having an ACN affects the comparative effectiveness of CRC screening tests, and, thus, is relevant information for making a screening test decision. Colonoscopy has higher effectiveness in patients who have a high probability of having a current ACN because of the larger chance that colonoscopy will identify a dangerous that should be removed.[7,13] Nearly all ACN are polyps rather than cancers (15:1 ratio in a recent study),[7] and polyps are considered the prime target of screening since they can be removed to prevent cancer.[12]

In patients whose probability of having a current ACN is lower, the burdens associated with colonoscopy may be difficult to justify since the chance of finding a lesion that should be removed is lower. And the chance that FIT or Cologuard will fail to identify a dangerous polyp or cancer is lower in a patient with lower baseline risk of ACN. FIT and Cologuard are approved for all average risk patients because they provide long-term risk reduction in colorectal cancer that rivals colonoscopy.[31,32] Still, failing to identify a polyp or cancer in the colon is a negative outcome of screening (a "false negative"),[32] so it is important that the chance of this occurring is smaller in patients with lower baseline risk of ACN.

Validated, usable rules for estimating the probability of current ACN in average risk patients are available. Our study utilizes a prediction rule that was validated for individuals receiving their first screening colonoscopy who do not have a risk factor that would place them at elevated risk for CRC (Imperiale et al. 2015).[7] **Table 1** shows the risk level and percent of patients placed in each category in a validation set of 1467 patients.[7]

TABLE 1

Individual's Risk level	Probability of current ACN	Percent of Patients
Very low	2%	8%
Low	4%	45%
Intermediate	10%	30%
High-average	22%	15%

The rule has three advantages over previous rules: First, it calculates risk of ACN using variables that are easy to collect: age, gender, smoking history, waist circumference, and family history. Second, the Imperiale rule identifies a wider range of probabilities in chance of having ACN than previous rules.[11,33-37] Third, the Imperiale rule classifies a significant percentage of average-risk patients into high-average and low risk. Fully 53% of the population have low or very-low ACN-risk, and 15% have high-average risk.

This risk stratification has clear implications for the comparative effectiveness of tests:

- Probability that screening colonoscopy will find an ACN: The chance of identifying and removing an ACN is five-times higher when performing colonoscopy in an individual with high-average of ACN (22% chance) than in someone with low risk (4% chance), and 10-times higher than an individual with very low risk (2% chance).

- Probability that a single application of FIT will fail to identify an ACN: Performing a FIT on each member of a high-average risk population will fail to identify ACN in about 11% of individuals, vs. just 2% of individuals in a low-risk population, and 1% in a very-low-risk population.

A patient's chance of current ACN, therefore, impacts test choice in a way other calculations do not. Some calculators, such as the NCI's CRC Risk Assessment Tool,[38,39] provide an estimate of future risk of CRC, but such information has no direct link to selecting a test: Having a chance of cancer in the next 10 years of 0.5% vs. 3% – the probabilities for the lowest quintile and the highest quintile for the NCI CRC risk tool[40] – does not clearly support one test over another.

Potential to improve healthcare decisions and outcomes: Our study will fill gaps left by previous studies in two key ways. First, it will use the Imperiale rule, which provides a more robust discrimination among average risk patients in their risk for current ACN.[7] Second, the personalized risk message for patients and providers explains how current ACN risk can inform choice of screening test.

Disclosing information about a patient's risk of having a current ACN has potential to increase uptake of screening. Letting patients know that their chance of having an ACN is low can support decisions to choose and complete the FIT test. Knowing that a patient who prefers FIT has low ACN risk may help providers overcome their hesitancy to order this test, by reassuring them that the chance of FIT's missing a cancer or dangerous polyp for this patient is low. Informing patients and providers that the patient has a high-average risk for an ACN can motivate discussion of screening colonoscopy and completion of that test.

At a system level, guiding patients at high-average risk toward colonoscopy and those with low-average risk to FIT could improve the efficiency of screening.[7,10,11,44] While colonoscopy is an effective screening test for all individuals with average risk from ages 50 to 75, it is more cost-effective for those with higher chance of ACN. If all eligible patients chose colonoscopy, endoscopy centers would be overwhelmed.[45-47] Given that the recently validated rule found that over 50% of the population had low- or very-low risk of having an ACN, the impact on reducing over-use of colonoscopy and the cost of CRC screening could be substantial.

Gaps in the evidence (RQ-1): Information about the probability of current ACN has not been incorporated into screening discussions for two reasons: First, randomized trials have not shown clear benefits of disclosing ACN risk. Second, no tools exist to quickly calculate patients' probability of ACN and convey that information clearly to patients and providers.

Skinner and colleagues (2015, 2016) – including Dr. Rawl, a member of our team – created and tested the tablet-based Cancer Risk Intake System, which identifies individuals' risk factors and screening barriers. Patients and their providers were given a printout summarizing the risk factors and barriers. High-risk patients, i.e. those with certain medical conditions or family history, were directed towards colonoscopy. Average-risk patients, i.e. without these risk factors, were told they could choose colonoscopy or stool blood testing. The tailored print out resulted in an increased level of discussion of CRC screening and increased uptake in patients eligible for screening.[41,42] Patients were not told their chance of an ACN, and those at average risk were not told whether their risk was high-average, intermediate, or low.

Schroy et al. (2016) studied the impact of providing information to average risk patients about their probability of having an ACN. In this study, 341 patients with average risk for CRC viewed a decision aid about CRC screening and half were randomized to be told their personal risk of currently having an ACN, either "low" (3%), or "intermediate/ high" (8%). All patients were given a handout with this information

to share with their healthcare provider.[43] This information had no significant impact on any of the measured outcomes, including screening choice.

These studies leave important gaps in the evidence (RQ-1). Skinner et al. (2015,2016) did not assess the impact of telling average-risk patients about having low vs. high-average risk for CRC and provided no guidance to average risk patients regarding the impact of risk factors or risk level on test choice. Schroy et al. (2017) provided average-risk patients with information about current probability of ACN but the difference between "low" and "intermediate/high" groups was just 3% vs. 8%, The small magnitude of this difference may have minimized impact. In addition, patients and providers in Schroy's study received no guidance about how to utilize ACN probability information to choose a screening test. Without an explanation why high risk for current ACN may be a reason to choose colonoscopy, or why low risk for ACN can support use of FIT, patients and providers may not make those connections. (RQ-4)

Patient and provider interest in research questions and outcomes: Patient interest (RQ-6, PC-1): In our pilot studies, patients have endorsed the importance of personalized information about CRC risk and probability of current ACN:

- Out of 57 patients who saw an estimate of their risk of current ACN, all 57 (100%) agreed or strongly agreed that "The information is important to me," and 55 (95%) agreed or strongly agreed that "I would recommend this information to other people."
- Out of 102 patients who saw a calculation of their personal risk of developing CRC in their lifetime, based on the NCI's Colorectal Cancer Risk Assessment Test,[38] and risk reduction provided by screening test, 100 (98%) agreed or strongly agreed that "The information is important to me," and 101 (99%) agreed or strongly agreed that "Other people should have similar information."

Our pilot studies also confirmed that viewing personalized information about CRC risk and probability of ACN increased intent to be screened and impacted test choice. These findings confirm our impression from our recently completed public deliberation, where patients expressed high interest in receiving quantitative information about the risk for CRC (RQ-6, PC-1). In a recent qualitative study, a patient said he would get FIT if he had low risk, since he really didn't want to go through colonoscopy anyway: "As much as I wanted to have the relief of knowing, I really didn't want to go through the pain."[50]

Provider interest: In a survey of 57 PCPs, 95% (n=56) preferred colonoscopy for CRC screening, but the majority considered patient risk level (67%) and patient preference (63%) as important factors in choosing a screening test.[10] When informed about the possibility of "an electronic risk index that could accurately stratify their average-risk patients into low-, intermediate- or high-risk categories for the likelihood of ACN," 97% stated they would be likely to use this tool "often" or "sometimes." In key-informant interviews, 9 PCPs said that risk stratification of patients eligible for CRC screening would be helpful to their discussions of screening (PC-1)(RQ-6).[10]

Two pilot studies by our team had similar findings. In our pilot testing of our provider messages about ACN risk, PCPs rated 26 out of 28 messages as very or somewhat helpful (See Methods, Choice of Comparators, p. 7, below) A qualitative study with 15 PCPs found significant support for use of the Imperiale ACN rule (RQ-6)(PC-1).[50] PCPs emphasized the importance of the rule providing an overall risk score that could help convince patients to be screened and the ability of such a rule to support discussions about CRC screening and consideration of FIT for some patients (RQ-6)(PC-1). One PCP said, that it "… seems more…appropriate...more rational, and maybe even a little bit safer, if we could avoid doing colonoscopies on patients with very low risk. It seems like a better balance of risk and benefit."[50] Some PCPs pointed to the similarity between this rule and risk calculations made on use of cholesterol medications. Potential barriers include limited time, questions about validity, and absence of national guidelines recommending its use. [50]

Cross cutting implications: Our decision aid and provider message for CRC screening exemplifies an approach that highlights providing **simple information** that is **directly linked to decisions** at hand. This approach could be a model far beyond CRC screening (RQ-1). The information we will gather about implementing a system for providing decision aids through the patient portal of EHRs, and for sending provider notifications, will apply to other areas

Engagement (PC-1), Dissemination, and Implementation: In developing this proposal, we actively engaged with *patients*, *partner healthcare systems leadership, providers, and staff, local patient advocacy groups, and national organizations involved in CRC screening* and we will continue this engagement throughout the project. A separate research protocol was developed to address our plan for studying the facilitators and barriers to implementing a system for providing decision aids to patients, and for sending provider notifications.

Patients: *Development of proposed study*: The patient advisory board of our previous study repeatedly asked about ways to calculate CRC risk levels for individuals and said that they would find such information helpful. Members of our patient advisory board were involved in development and pilot testing of the personalized-messages and decision aid.

- *Involvement in upcoming study*: Four of the patients who served on the patient advisory board in the last study will serve as **patient consultants** and will attend research team meetings and work independently in concert with the team. Patient consultants will review and edit recruitment letters, phone call scripts, decision aids, and outcome measures. They will also continuously review our information regarding providing decision aids through the EHR patient portal. Patient consultants will get input from family and friends at key points. (PC-1)
- *Dissemination*: Patient consultants will accompany other research team members to national meetings, and may serve as panel members or discussants. (PC-4)

Leadership of partner healthcare systems: *Development of proposed study*: IU Health and Eskenazi leadership and quality improvement teams have always worked closely with our research team on CRC screening projects due to our shared interest in increasing CRC screening uptake rate. More recently, we have developed the proposal to provide decision aids through the patient portal of the EHR systems (Epic at Eskenazi, Cerner at IU Health). Both institutions wish to use these portals more frequently in patient care. We have worked closely with the information technology teams at both institutions to develop this plan and pilot the system at Eskenazi. (PC-1)

- *Involvement in upcoming study*: In our previous studies, the quality improvement teams at IU Health and Eskenazi Health worked with the research team by serving on a community advisory board. A separate research protocol was developed to address our plan for studying the facilitators and barriers to implementing a system for providing decision aids to patients, and for sending provider notifications (PC-1)
- *Dissemination and Implementation*: Leadership at both institutions intend to implement research findings regarding how to use patient portals to distribute decision aids, with or without personalized information. (PC-4)

Providers and Staff of partner healthcare systems: *Development of proposed study*: Providers at IU Health and Eskenazi who participated in previous studies by serving on the stakeholder advisory board or allowing us to enroll their patients provided important input on developing this study. Providers also participated in pilot testing of the provider message.

- *Involvement in upcoming study*: *Decision aid*: Before initiating the study, staff and providers from participating clinics will view the decision aids and provide feedback on content and plan for providing to patients through the online portal, including timing in relation to an upcoming visit.

Changes will be made based on this feedback. A separate research protocol was developed to address our plan for studying the facilitators and barriers to implementing a system for providing decision aids to patients.

- *Involvement in upcoming study:* <u>*Provider notification*</u>: Providers will provide feedback on draft versions of the message and will identify preferred timing for receiving the message (i.e. how long before patient visits). A separate research protocol was developed to address our plan for studying the facilitators and barriers to implementing a system for sending provider notifications We will also quantify the percentage of provider notifications that were read by each provider and will evaluate characteristics of providers who opened a high percentage vs. a low percentage of messages, including elements of practices for high and low users, such as staff communications and leadership support. (PC-1)
- *Implementation:* Staff and providers involved in this engagement will potentially become champions and "super users" for future implementation of decision aids and provider notifications in their clinics. (PC-4)

<u>National organizations and local patient advocates</u>: *Development of proposed study*: The development of the proposed study has been informed by engagement with local and regional groups that have served as key partners previously, including the American Cancer Society and Little Red Door cancer agency. We have had involvement of national leaders such as co-investigator Brian Zikmund-Fisher, PhD, and consultants Paul Han, MD, MA, and Michael Barry, MD. For preparing the current resubmission, Jon Keevil, MD, Vice President for clinical decision support at EBSCO provided an industry perspective. We benefited from input from leadership of national groups focused on CRC screening, including Richard Wender, MD, Chair of the National Colorectal Cancer Roundtable, and Chief Cancer Control Officer of the American Cancer Society, and David Lieberman, MD, President of the American Gastroenterology Association.

- *Involvement in upcoming study:* These individuals and groups have agreed to remain involved in the study as a National Engagement and Dissemination Team, which will hold three-times-per-year teleconferences, to discuss the design, conduct, results, and potential implications of our study. If the study is funded, additional members will be recruited. Regional group representatives will also participate in teleconferences. Dr. Zikmund-Fisher and Dr. Han will bring a national perspective to the research team and will provide external review and edits for all materials and plans.

Implementation: This broad involvement will keep our focus on implementation throughout the project. The representatives of prominent national groups will provide avenues for dissemination. Through these groups, we will make the decision aids, provider notifications, and materials for distribution of the decision aid by the electronic health record, available to interested healthcare systems and providers. (PC-4)

2.0 Approach

Study Aims: Our <u>*long-term goal*</u> is to increase uptake of CRC screening by informing and improving patient and provider discussion and decisions. The <u>*main objective*</u> of this study is to test whether providing patients and their providers with personalized messages about ACN risk results in higher screening uptake and higher decision quality (i.e., informed choice and receipt of the preferred screening test), compared to an approach that does not utilize ACN risk.

Aim 1: To measure the impact on patient decision quality and screening uptake of providing patients and their providers with personalized messages about the patient's current risk of having advanced colorectal neoplasia (ACN).

Aim 2: To examine mediators and moderators of the interventions' effectiveness.

To achieve Aim 1, we will test the following hypotheses:
Primary hypotheses:
1. The proportion of patients who make a **high-quality decision** and **complete screening** at six months will be higher:

1.1 for patients who receive the personalized message than for those who do not, and
1.2 for patients whose providers receive the personalized message than for those whose providers do not.

Secondary hypotheses:
2. Among patients with low risk of ACN, the proportion who make a **high-quality decision** and **undergo a stool blood test (FIT)** by six months will be higher

2.1 for patients who receive the personalized message than for those who do not, and
2.2 for patients whose providers receive the personalized message than for those whose providers do not.

3. Among patients with high-average risk of ACN, the proportion who make a **high-quality decision** and **undergo a colonoscopy** by six months will be higher

3.1 for patients who receive the personalized message than for those who do not, and
for patients whose providers receive the personalized message than for those whose providers do not.

3.0 Outcome Measures/Endpoints

Choice of Outcomes (PC-3, RQ-6): The primary outcomes are screening uptake and decision quality, each of which is essential to providing high-quality and patient-centered care.

- Screening uptake will be defined as performance of colonoscopy, FIT, or another approved screening test within six months after enrollment, as documented in the EHR, as in our previous study.[51]
- Decision quality will be defined by the multi-dimensional measure of informed consent (MMIC),[53] where a high-quality decision is one where the individual has adequate knowledge regarding the available options and undergoes the intervention that he or she has chosen or that fits his or her values ("value concordance") (PC-3)(RQ-6). Sepucha et al. (2018) recently used the MMIC approach in the Colorectal Cancer Screening Decision Quality Instrument (CRC-DQI).[54] We will identify knowledge and the patient's intention to be screened shortly after a provider visit (T2). We will measure concordance between the test choice at T2 and screening test underwent, if any, within six months after enrollment (T3).[55-58]

Increasing screening uptake is an essential outcome since screening saves lives (RQ-6). Providers and healthcare institutions aim to get their patients screened, heeding the ethical principle of beneficence.[59] Our partner healthcare institutions have repeatedly expressed their desire to increase their screening rates(RQ-6). We heard the same message – the importance of getting patients screened – from lay people participating in our public deliberation exercise (RQ-6).[60] Both patients and lay people have emphasized, from the beginning of our work on CRC screening, and in the public deliberation, the importance of improving decision quality about CRC screening.(RQ-6) Patients who view decision aids as part of our studies often learn about FIT for the first time, and often respond that there should be more public awareness of this option.(RQ-6)

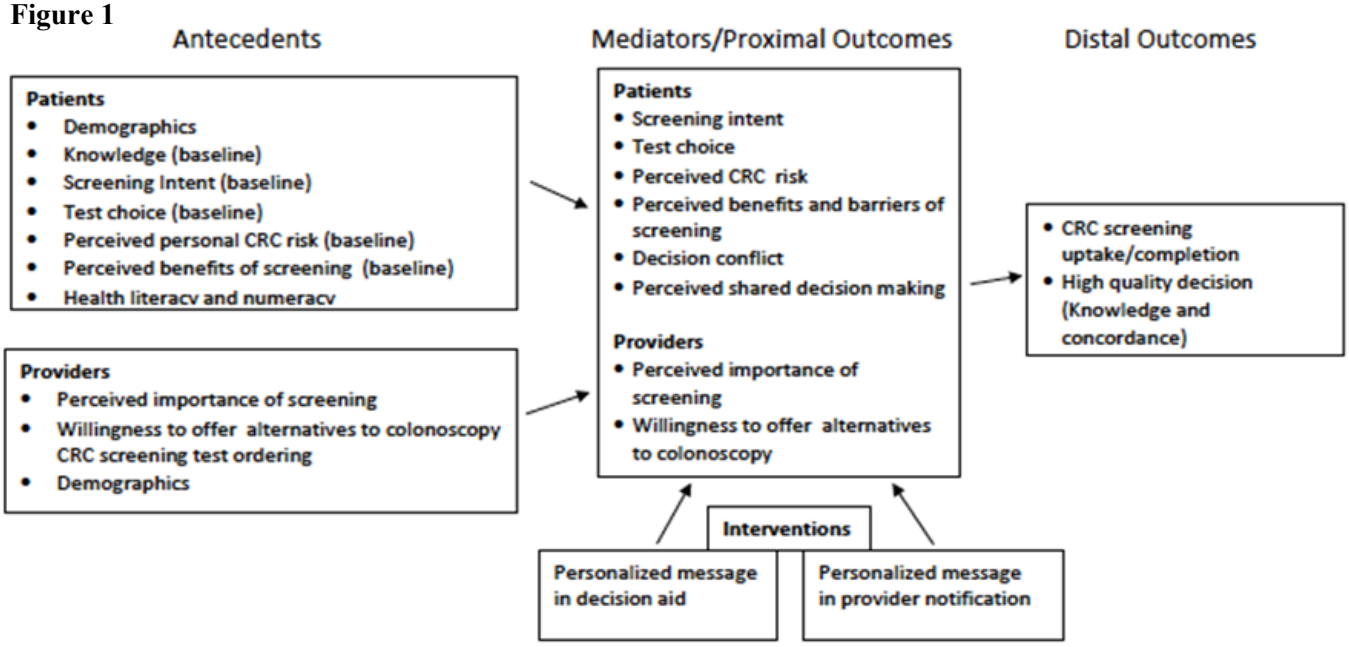
We chose not to make decision conflict[61] or shared decision-making distal outcomes, due to our focus on screening uptake and quality of decision making. However, we will collect these subjective measures as potential mediators for the primary outcomes. Improved outcomes may result from patients feeling

more supported in their decision making, as captured by the decision conflict scale,[61] or feeling that they participated in shared decision making with their healthcare provider, as captured by one section of the CRC Screening Decision Quality Instrument developed by Sepucha et al (2018).[54]

Theoretical framework: See **Figure 1**: (CI-1) Our theoretical framework is based on the Health Belief Model,[62] which has been previously applied to research on CRC screening uptake.[63-65] We expect the personalized message to impact patients at low risk, intermediate risk, and high-average risk, as described below:

- Low risk: For patients at low risk, *patients* and *providers* who view the personalized message will have increased perceived benefit of FIT and lower perceived barriers (i.e. concern over false negative result). These effects will increase the proportions of patients intending to be screened and to undergo FIT, and the proportion of providers who are willing to order FIT for patients who choose that test. Agreement between the patient's choice and the provider's ordered test will increase uptake (Hypothesis 1.1 and 2.1),[43] and higher concordance between patient choice and completed FIT will increase decision quality as measured by the MMIC (Hypotheses 1.2 and 2.2).(RQ-4)(CI-1)
- High-average risk: For patients with high-average risk, *patients* and *providers* who view the personalized message will have *increased perceived susceptibility* to CRC due to the high probability of a current ACN (22%) and *increased perceived benefit* of colonoscopy. These effects will increase the proportions of patients intending to be screened with colonoscopy, and the proportion of providers who order colonoscopy for patients who choose this test. This will result in increased uptake of screening (Hypotheses 1.1 and 3.1) and increase concordance between patient choice and performed test, which will increase decision quality as measured by MMIC (Hypotheses 1.2 and 3.2).(RQ-4)
- Intermediate risk: For patients with high-average risk, *patients* and *providers* who view the personalized message will have *increased perceived susceptibility* to CRC due to the significant probability of a current ACN (10%). This will increase patients' intention to be screened, providers' interest in discussing CRC screening and ordering a test, and successful follow through by patients, which will contribute to an increase in uptake of screening (Hypothesis 1.1) and in concordance and thus decision quality as measured by MMIC (Hypotheses 1.2).(RQ-4)(CI-1)

Figure 1



3.1 Primary Outcome Measures

The primary outcomes are screening uptake and decision quality, each of which is essential to providing high-quality and patient-centered care.

- Screening uptake will be defined as performance of colonoscopy, FIT, or another approved screening test within six months after enrollment, as documented in the EHR.
- Decision quality will be defined by the multi-dimensional measure of informed consent (MMIC),[53] where a high-quality decision is one where the individual has adequate knowledge regarding the available options and undergoes the intervention that he or she has chosen or that fits his or her values ("value concordance"). (PC-3, IR-4)
    - Knowledge (T2) will be assessed by a 12-item test made up of 6 multiple choice questions and 6 true-false questions that was updated from what we used in our previous study to reflect changes in screening guidelines. Adequate knowledge = 9 correct
    - Concordance (T3) will be measure between the test choice at T2 and screening test underwent, if any, within six months after enrollment(T3).

3.2 Secondary Outcome Measures

Patients: Data will be collected from patients at four time points: before they view the decision aid (T0); immediately after they view the decision aid (T1); aiming for 4-7 days after their appointment with their provider (T2); and six months after enrollment (T3).

- *Screening Intent* (T0, T1, T2): Intent to be screened for CRC with any test ("Screening Intent"), will be measured with 1 item: "Do you plan to get any type of colon test within the next 6 months?" and has a response option of: 5=Definitely, 4=Probably, 3=May or May not, 2=Probably not, and 1=Definitely not. This measure has been used in previous studies by our research team (PC-3, IR-4).[51,52]
- *Test choice* (T0, T1, T2) (PC-3, IR-4): As in our previous studies:[51,52]
    - For those who answer *Screening Intent* with "Definitely not," "Probably not," or "May or may not," *Test Choice* is categorized as No screening.
    - Those who answer *Screening Intent* with "Probably" or "Definitely" have *Test Choice* categorized based on their answer to a single item: "If you have a colon test, which one would you choose?" Response options are: Stool test (FIT or Cologuard), Colonoscopy, Another test, or Don't know.
- *Perceived CRC risk* (T0, T1, T2):
    - *Perceived personal CRC risk* will be assessed with a three-item scale, modified from items originally developed by Champion to measure perceived breast cancer risk[78,79] and used by members of our team in multiple projects.[51,52,69] Each item uses a four-point response option, where 1 = very unlikely and 4 = very likely, to assess participants' beliefs about how likely they are to get CRC in the next 5 years, in the next 10 years and sometime during their lifetime. Cronbach alpha was 0.90 in our recent study. (PC-3, IR-4)
    - *Perceived comparative CRC risk* will be assessed with a single item measuring perceived comparative risk,[66] which asks "Compared to other women/men your same age, would you say your change of getting colon cancer in the next 10 years is higher, about the same, lower, or don't know?" (PC-3, IR-4)
- *Decision Conflict* (T0, T1, T2) will be assessed with the low literacy version of the Decision Conflict Scale, a ten-item instrument that assesses patients' subjective feeling regarding the decision process over five areas and has been used widely in studies of decision aids (PC-3, IR-4).[61,70]
- *Perceived Shared Decision Making* (T2) will be assessed with two measures. Patients will first answer five items adapted from the Shared Decision Making Process_4 Survey. This tool is a National Quality Foundation Measure used to assess the extent to which patients are involved in the decision-making process (PC-3, IR-4).[54] Patients will also respond to the 3-item CollaboRATE measure that assess three key areas of shared decision making; 1) explaining the health issue; 2)

asking for patient preferences; and 3) incorporating patient preferences into the decision. Each item uses likert response options ranging from "no effort was made" to "every effort was made".[73, 74]

- *Numeracy: Subjective numeracy* will be assessed at T0 with the Subjective Numeracy Scale (SNS) – short form, a validated instrument that involves 3 Likert-style questions.[67,71,72]
- *Literacy* (T0) will be assessed using a 3-item health literacy scale (IR-4).[75]
- *Demographic data* (T0) (including age, gender, income, education), as well as data on previous MD CRC screening recommendations, will be assessed utilizing a survey that has been used by our team and other researchers in multiple studies of CRC screening.[51,69]

3.3 Additional Measures

- Program evaluation: We will evaluate the presentation with 7 investigator created items at T1 and 2 items at T2 for all patient-participants and an additional 5 items at T1 for those patients who viewed the personalized risk information. The items will measure satisfaction and usefulness of the presentation as well as the perceived trustworthiness of the information.
- Provider Intervention evaluation: We will evaluate the personalized message with an investigator created survey for all providers randomized to receive the screening reminder + personalized message. The items will measure how much the personalized information was helpful, how much they would use it if integrated into the electronic health record (EHR), what type of patient they would use the informtion
- *Impact of COVID-19 on screening preferences and intentions* (T2): will be assessed with one open-ended question: "How has the COVID-19 pandemic affected your decision about getting screened for colorectal cancer?" Patients also will be provided with a list of common factors affecting decisions from which they can check all that apply.
- *Reasons for test preference, test choice, and follow-up for discordance* (T2): Patients will answer an open-ended question about their intent to be screened and test preference. Patients whose screening intent or test choice changed from T1 will be asked to explain the reason for the change.

Providers: Data collection from providers will include:

- *Ordering of CRC screening test* will be assessed by reviewing the EHR for orders for FIT, colonoscopy, or other CRC screening test for each patient at six-month follow up.
- *Opening of provider notification* will be assess for providers by reviewing the EHR.
- *Demographic data* (including age, gender, time in practice at enrollment) will be assessed using the AMA Physician Datafile.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

Patients will be eligible if they are:

- age 50-75 years
- have not had colonoscopy performed in last 10 years, sigmoidoscopy in last 5 years, or fecal occult blood testing (FOBT or FIT) in the last year, or Cologuard in the last 3 years
- have not had a colonoscopy since age 50 years
- have a scheduled appointment with a provider who agreed to participate in the study and approved approaching their patients.

Providers will be eligible:

- if they are a physician (MD or DO), nurse practitioner (NP), or physician assistant (PA) practicing at one of our research sites

4.2 Exclusion Criteria

Patients will be excluded if they are:

- undergoing workup for symptoms consistent with CRC, such as unexplained weight loss, change in bowel habit, or rectal bleeding
- have a diagnosis or medical history conferring elevated risk for CRC including a previous adenomatous polyp or CRC, inflammatory bowel disease, high-risk syndromes, or a significant family history of CRC (two or more FDRs with CRC or one FDR with a CRC diagnosis prior to age 60)
- are unable to speak and read English
- previously participated in any research projects regarding colorectal cancer screening or colonoscopy including, but not limited to our previous studies.
- Members of the study team will not be participating in the study; therefore, patients who have a scheduled appointment with any member of the study team will not be eligible.

Providers will be excluded if they are:

- None

5.0 Study Design

We will conduct a 2x2, randomized, controlled trial (**see Table 2)** to compare decision quality and screening uptake in four groups of patients who view a decision aid:

- Group 1) without the personalized message and whose providers do not receive the personalized message (control group)
- Group 2) with the personalized message and whose providers do not receive the personalized message;
- Group 3) without the personalized message and whose providers receive the personalized message, and
- Group 4) with the personalized message and whose providers receive the personalized message.

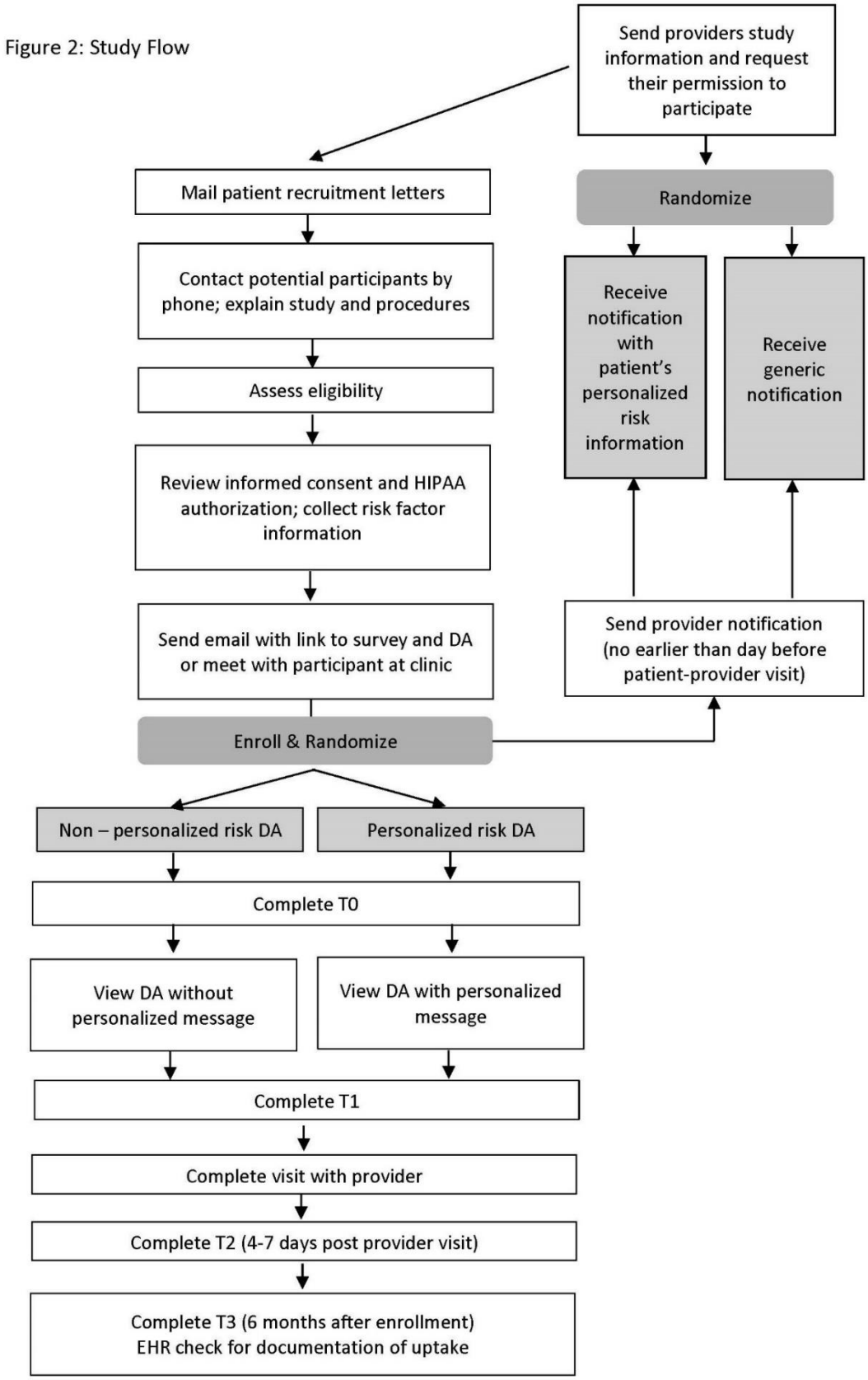
Table 2

	Patient views:	
Provider receives:	Decision aid WITHOUT personalized message	Decision aid WITH personalized message
Screening reminder	Group 1	Group 2
Screening reminder + Personalized message	Group 3	Group 4

We have chosen a 2x2 design in order to separately evaluate the impact of personalized messages provided to patients and to providers. It is essential to evaluate these two interventions separately due to the expense and effort required for implementing either of them. We will cluster patients by provider in order to avoid the danger that providers who received the message for some of their patients would use similar methods for patients for whom they did not receive the message.

Comparators: Our study involves three comparators: (1) a CRC screening decision aid without a personalized ACN risk message, (2) a CRC screening decision aid with a personalized ACN risk message, (3) A provider message with personalized ACN risk information.

Study Flow Diagram:



6.0 Enrollment/Randomization

Patients: We will recruit patients from primary care clinics from two healthcare systems in Central Indiana: the IU Health Physicians' primary care practices of the Indiana University Health system (currently 34) and the primary care practices of Eskenazi Health (currently 9). These clinics serve a wide range of socioeconomic groups, including rural, upper-income suburban, middle-income urban/ suburban, and lower-income urban (including 7 Federally Qualified Health Centers). Nineteen of the IU Health practices are outside of Indianapolis, and 4 are > 40 miles from the academic health center. (PC-2)

Clinical Information Specialists at IU Health will identify potentially eligible patients who have an upcoming appointment using a query of their electronic health record (Cerner) and will share that list with the research team weekly or biweekly. Eskenazi Health's potentially eligible patients will be identified by the Regenstrief Data Core, also on a weekly or biweekly basis. Both health systems will save a list of potentially eligible patients, along with their medical record number (MRN), street address, phone number, upcoming clinic appointment date and healthcare provider, and EHR patient portal enrollment status in a secure server accessible by the project manager and data manager. These lists will be updated on a regular basis throughout the recruitment period.

The research team will send potentially eligible patients a letter of introduction explaining the study (see Notes & Attachments for letter and brochure). The letter will also include a phone number that patients can call to opt out of being contacted. A week later, the research assistant will call patients (see Notes & Attachments for phone script) who have not opted out to explain the study and answer questions about study requirements, potential risks, and compensation. If the patient is interested in joining, the research assistant will confirm eligibility. If the patient is eligible, the research assistant will review the study information sheet (SIS) and HIPAA authorization. The SIS and HIPAA authorization will be emailed to the participant after the recruitment call with instructions and encouragement to contact the study team with questions. If the patient prefers, the research assistant can schedule a follow-up call to discuss the SIS and HIPAA authorization after the patient has had time to receive and review. For those patients who refuse to be assessed for eligibility, the RA will record reasons for refusal.

Participants will be offered three options to access the decision aid and complete the first two surveys (T0 and T1). They may choose to receive an electronic link: (i) through the EHR patient portal (preferred), (ii) by email, or (iii) on an iPad provided at the patient's clinic. For systems (i) and (ii), the research assistant will provide assistance as needed by phone when the patient opens the link or in the clinic for those who wish to use the iPad (method iii).

The electronic link will take the patient to a Qualtrics database. A randomization scheme, generated by our Biostatistics team, will be connected to the Qualtrics database. When the participant enters Qualtrics, this will trigger Qualtrics to assign them to the Control group (view the non-personalized DA) or the Intervention group (View the personalized DA).

Research team members interacting with the participants will be blinded to patient assignment. The patients will be blinded to assignment of their provider.

Providers: The providers will be identified through each health system's provider directory, and confirmed and updated by the practice administrators. All eligible providers will be sent a letter and study information sheet explaining the study (see Notes & Attachments for letter and SIS), and be given the opportunity to let the research team know if they choose not to participate. Providers who agree to participate will be randomized to the Control group (receives a generic message) or the intervention

group (receives patient's ACN risk). The providers will be randomized based on a randomization scheme generated by our Biostatistics team.

The research team will not be blinded to provider assignment as they will need to know which notification to send. Providers will know that their patient enrolled in the study; however, the provider will be blinded to the patient's group assignment.

7.0 Study Procedures

Since the goal of the proposed research is to improve patient decisions regarding screening and prevention by testing an innovative approach to informing patients and their healthcare providers about personal risk for colorectal cancer, we require the involvement of both patients and healthcare providers.

7.1 Interventions

Patients:

Decision aid without personalized message (RQ-5): For the study, we have modified the "verbal" decision aid designed and tested in our study supported by PCORI (CDR-1403-11040). In this study, 688 patients eligible for screening viewed a decision aid that provided extensive information about CRC screening, including baseline risk of lifetime CRC mortality and incidence (no screening), risk reduction provided by colonoscopy and FIT, sensitivity of colonoscopy or FIT, and rate of FIT turning positive (requiring colonoscopy) and of complications from colonoscopy.[51] Half the patients viewed a decision aid presenting this information using numbers and icon charts (quantitative arm); the other half viewed a decision aid presenting the information using only verbal descriptions (no numbers) (verbal arm).[51]

Viewing either decision aid in this project led to significant increases in mean intent to undergo screening (3.94 vs. 3.52, $p < .001$) and to undergo FIT (3.41 vs. 3.05, $p < .001$), both on a five-point scale, and lower decision conflict (18.8 vs. 39.5, $p< .001$). Compared to participants in the Verbal arm, those in the Quantitative arm had a larger increase in intent to undergo FIT ($p = 0.011$), and were more likely to switch their preferred test from non-FIT to FIT (28% vs. 19%, $p =.010$).[51] There was no difference in uptake of screening at six months (about 30% in both arms) or test choice (RQ-5).

The current study's *decision aid without personalized message* consists of a PowerPoint presentation converted to mp4 (video) with text, photos, and an audio track, that is advanced by the viewer and can be viewed online. It begins with a 60 sec video on CRC screening produced by the Centers for Disease Control and Prevention (CDC), followed by slides summarizing the advantages and disadvantages of colonoscopy and stool testing with the fecal immunochemical test (FIT)[51] and DNA+FIT (Cologuard). (See **appendix** for DA script)

Decision aid with personalized risk message (RQ-5): For the current study, we have modified two decision aids developed and tested in previous studies. Initially, we developed a decision aid that provides a personalized risk message based on the ACN risk rule to be used in this trial[7] and pilot tested it with 96 patients (RQ5). Viewing this decision aid resulted in a significant increase in mean intent to get screened (3.22 vs. 2.68, $p < .001$), intent to have FIT (2.59 vs. 1.98, $p < .001$), intent to have colonoscopy (2.82 vs. 2.64, $p = .002$), and lower decision conflict (35.9 vs. 61.9, $p < .001$), compared to before viewing the decision aid. Of note, the groups with low and very low risk for ACN were combined into one group ("low risk"). Individuals with low ACN risk (n=16) were randomized to view a description of the advantages of FIT for people with low risk. Patients in this group who viewed this description had a larger increase in intent to undergo FIT than did those who did not view the information (-0.06 vs. +1.00, $p = .001$).

Patients in this pilot study received messages whether their risk of current ACN was low, intermediate, or high-average based on the ACN prediction rule, but did not receive more specific information about their ACN risk (i.e. 4%, 10%, or 22%).

Based on our previous studies showing mildly beneficial effects of providing quantitative information,[51,52] we modified the decision aid to include an icon chart depicting this probability as a frequency, and we pilot tested that decision aid with 9 patients. While this small pilot test did not allow formal statistical testing, intent to be screened was increased or unchanged after viewing the decision aid, compared to beforehand, for all patients.

The current study's *decision aid with personalized message* will first present the *decision aid without personalized message* followed by additional PowerPoint slides converted to mp4 (video) with text, photos, and an audio track briefly explaining the risk tool, the participant's score on the 5 risk factors, total score, ACN risk, and implications for screening and test choice. (see Appendix for DA script)

The decision aid without personalized message is approximately 10 minutes and the additional slides with the personalized message take approximately another 4 ½ minutes to view.

Providers:

Provider personalized ACN risk message (RQ-5): We designed and pilot tested a personalized message for providers that discloses:

- the patient's ACN risk: low (combining low and very low categories), intermediate, or high-average,
- the predicted frequency of ACN on an icon chart: 4 per 100; 10 per 100; or 22 per 100, and
- implications for screening decision and test choice.

The personalized message was slightly modified from one tested by Skinner et al. (2015, 2016), which was found to increase discussion of CRC screening and uptake in some groups.[41,42] Both messages list patient risk factors for CRC and guideline-consistent recommendations for screening. Our message differs from Skinner's in that it classifies the probability of having a current ACN as low-average, intermediate, or high-average, displays the probability on an icon chart, and recommends FIT for patients at low risk and colonoscopy for those at high-average risk. Like Skinner's, our message specifies that both tests are acceptable for average-risk patients.

We tested the modified provider message with six primary care providers (5 MDs and 1 NP), each of whom viewed messages for four or five patients from their clinic who participated in the pilot testing of the final decision aid (28 evaluations total). Providers estimated the patient's risk of current ACN (low, average, or high) before and after viewing the message, and they changed their estimate in 17 of 28 evaluations (61%). The providers' recommended screening test (colonoscopy, FIT, or either) changed after viewing the message in 16 of 28 evaluations (57%). For 26 of 28 evaluations, providers rated the information about ACN risk very helpful or somewhat helpful (PC-1).

For the current study, we have further modified the provider message based on feedback from IU Health and Eskenazi providers. The notification will include the patient's ACN risk (very low, low, moderate, high-average) and implications for screening decisions and test choice. Links to a web landing page containing a more detailed explanation of the risk tool and additional references will be included. (see Appendix for notifications and web landing page)

Providers randomized to the control group will receive a message informing them that their enrolled patient is due for CRC screening.

Providers will receive the message by email linked to the EHR system. The message will be sent by the research team within 24 hours of the provider's appointment with the enrolled patient.

7.2 Data Collection

Patients: Potentially eligible patients will be sent a letter of introduction and explanation about the study. The letter will inform patients that they will receive a call about the study in the next few days and will include a telephone number to call if they wish no further contact. A week after letters are mailed, the research assistants will call patients who have not called the "opt out" number. The research assistants will explain the study and answer patients' questions about study requirements, potential risks, and compensation. If the patient is interested in joining, the research assistant will confirm eligibility. If the patient is eligible, the research assistant will review the study procedures, the informed consent document and HIPAA authorization, and obtain verbal consent and authorization.

The research assistant will then collect the data to calculate the participant's risk for having an advanced colorectal neoplasm (ACN). This involves confirming gender, age, and family history of colorectal cancer. The research assistant will ask the patient for their smoking history and calculate pack years (none, < 30 pack years; ≥ 30 pack years). The research assistant will also ask the participant for their waist size (for men: under 37 ½ in; 37 ½ -47 in; > 47 in; and for women: < 34 ½ in; 34 ½ - 43 ½ in; > 43 in).

The research assistant will discuss with the participant which of the 3 options they prefer to access the decision aid and survey: (i) through the EHR patient portal, (ii) by email, or (iii) on a iPad at a primary care practice. Based on that discussion, the research assistant will send the participant the link to their survey and decision aid. The research assistant can be available by phone or in-person at the practice as needed to assist participants in accessing the survey and decision aids. The research assistant will encourage participants who choose to access the surveys and decision aid on their own device to do so in a quiet location free as possible from distractions.

The email sent to participants will review the study procedures, who to contact with questions, and the unique link to their survey in Qualtrics. When the participant clicks the link, they will be taken to Qualtrics and the baseline survey (T0). After the participant completes T0, Qualtrics is programmed to stream the appropriate decision aid for that participant. When the decision aid completes, the post-intervention survey (T1) will display. Following completion of T1, the participant will be automatically sent a confirmatory email thanking them for completing this part of the study, reminding them of the next study contact, and who to contact with questions.

The baseline (T0) and post-intervention (T1) surveys are planned to take about 10 minutes each to complete. The control decision aid is approximately 10 minutes long and the intervention decision aid is approximately 15 minutes long (see Appendix for T0 and T1 surveys).

Research assistants will start contacting participants approximately four days after the participant's provider visit to complete the post-provider visit (T2) survey. Research assistants will aim to start collecting the T2 data four days after the provider visit; however, if the patient requests contact sooner due to scheduling conflicts, the research assistant will contact the patient as requested. Research assistants will first attempt to collect the T2 data over the phone; however, if unsuccessful or if the participant prefers, the research assistant can email the participant a link to complete the survey online in REDCap.

The post-provider visit (T2) survey is planned to take about 15 minutes (see Appendix for T2 survey).

Research assistants will start contacting participants 6 months after study enrollment to complete the 6-month follow-up (T3) survey. Research assistants will first attempt to collect the T3 data over the phone; however, if unsuccessful or if the participant prefers, the research assistant can email the participant a link to complete the survey online in REDCap.

The 6-month follow-up (T3) survey is planned to take about 15 minutes (see Appendix for T3 survey).

The patient's medical record will be queried for documentation of colonoscopy, FIT, or another approved screening test within six months of study enrollment. Regenstrief Data Core will query the electronic health records (EHR) for screening uptake for both Eskenazi Health and IU Health patients. Research assistants will confirm discrepancies between query results and patients' self-reported uptake.

Providers:
The Regenstrief Data Core will query the EMR for orders for colonoscopy, FIT, or other approved CRC screening test entered by each provider for their enrolled patients. They will also query the EHRs for the read status for all the provider notifications that were sent. Demographic data will be assessed using the AMA Physicians Datafile.

8.0 Reportable Events

If a participant experiences an adverse event that occurs in greater frequency or severity than previously known, this will be reported to the IRB either as a prompt report if it meets reporting criteria, or at time of study closure.

9.0 Data Safety Monitoring

Dr. Peter H. Schwartz, principal investigator will have ultimate responsibility for monitoring the safety and security of the participants and data. Dr. Schwartz and his study team will engage in quality improvement practices beginning with development and then with ongoing review of study procedures. The Co-Investigators will be actively involved in quality assurance activities including monitoring of recruitment, adherence to eligibility criteria, adherence to study protocol, quality of data entry, and adherence to any adverse event reporting.

10.0 Statistical Considerations

Sample Size Justification: This trial is powered for the two primary hypotheses. For Aim 1, we expect exposure to either personalized message will increase uptake from 30%, which was the uptake at six months seen in our current PCORI project, to 40% and the combined effect to be additive (i.e. no interaction between the interventions). We believe a 10% increase in uptake is a minimally important difference to detect. An earlier study found that patients who viewed a personalized message about risk of colorectal cancer had a 9% higher uptake than did those who viewed a non-personalized message (CI-2).[41] We believe our intervention will have greater impact, due to its encouraging low-risk individuals (50% of patients)[7] to use a non-invasive test. An earlier study found that individuals due for screening who were offered a non-invasive test had a 31% higher rate of screening than those offered just colonoscopy (69% vs. 38%)(CI-2).[5] To detect an effect of 10% increase (odds ratio of 1.55) with a power

of 80% (two-sided α= 0.05) a sample size of 732 subjects (183 per group) is needed for the Wald test for either patient or provider message main effect in a logistic model if patient outcomes were independent. To account for clustering due to randomization by provider, we inflate the sample size based on the design effect. We assume an intraclass correlation of .05 for provider, and average number of subjects per provider of 8. (RC-3) We will allow for an attrition rate of 10%. This results in a final sample size of 1100 (275 per group). For the informed choice outcome, we expect exposure to either personalized message would increase informed choice from 20%, the outcome in our current PCORI project, to 30% (odds ratio of 1.71) and the effect to again be additive. This leads to an initial sample size of 604 total (151 per group) before accounting for inflation and attrition, which is less than for uptake. Thus, the sample size needed for both outcomes is 1100 (275 per group, 130 providers). These recruitment goals are readily achievable based on the INFORM study. Aim 2 is considered exploratory because we don't have sufficient preliminary data to estimate all effect sizes; however, we will have sufficient power for some hypotheses. (IR-1)

Analytic plan: Preliminary analyses will compare baseline demographic information across the four groups using means and standard deviations for continuous variables and frequency distributions for categorical variables. We will adjust for those characteristics in subsequent analyses if significant differences emerge at a conservative level for inclusion of a covariate ($p<.20$). Characteristics of participants who don't complete T1 and/or T2 will be compared with those who remain to determine what biases may exist. The above analyses will be conducted using ANOVA, chi-square tests, or exact or non-parametric equivalents. If there appear to be biases in dropout, we will conduct pattern mixture models analyses to see how the results could change based on the missing data assumption (IR-5, MD-2, MD-3, MD-4). Primary analysis of outcomes will employ an intent-to-treat analysis. For Aim 1, our primary hypotheses will be tested using logistic regression models with the outcomes of informed choice and uptake (both yes/no outcomes) and main effects for: 1) patient receipt of personalized message; and 2) provider receipt of personalized message. A random effect for provider will be included to account for the clustered randomization. We will test for an interaction effect, but do not expect one so have not powered the study for an interactive effect. The secondary hypotheses (planned subgroup analyses with low risk group) will be tested using the same model type (HT-2, HT-3). The secondary hypotheses are considered exploratory. For Aim 2, mediation effects (RQ-6) will be estimated in a logistic regression setting, fitting the appropriate mediation models using MPlus[76] and then testing indirect effects using the percentile bootstrap approach to estimate the indirect effect.[77] For primary analyses, we will fit models that estimate the effects of either or both of the interventions relative to control. Moderators (RQ-4, HT-1, HT-2, HT-3, HT-4) will be identified by significant interaction terms in the regression models from Aim 1.

11.0 Statistical Data Management

We will create a secure web-based system to capture study data using the REDCap and Qualtrics database management system. We will review and process data using multiple verification and edit checking programs (e.g. range-checks, missing data reports). We will also conduct rudimentary analyses to ensure that the data have been properly collected and to identify any outliers or errors. A consort diagram will be constructed for reporting that accounts for all missing data (IR-5, IR-7, MD-1, MD-4).

12.0 Privacy/Confidentiality Issues

Potential Risks

A breach of confidentiality is always a risk with minimal risk studies. In addition, participating in a research study and answering questions may cause anxiety.

For patient-participants, the information presented regarding risk of colorectal cancer and choice of screening test may cause patient-participants to become confused or anxious. Finally, after participating in this study, patients may make a different decision regarding colorectal cancer screening than they would have made if they had not participated in the study. This is true, of course, in any study that provides patients with information regarding medical conditions or available interventions. Participation in the study still counts as carrying minimal risk, though, since (a) all patient-participants will receive evidence-based, high quality information about colorectal cancer and screening, and (b) each of the recommended choices are approved, available screening tests with proven ability to reduce morbidity and mortality of colorectal cancer.

Protecting against, or Minimizing Potential Risks

For both patient and provider participants, all information required for recruitment and tracking will be stored in a HIPAA-aligned database accessible only by authorized study team members primarily the recruiters. All team members will adhere to our institution's HIPAA policy and use of protected health information. All data provided by the patient and provider participants will be collected and stored in a separate HIPAA-aligned database accessible only by authorized study team members. Authorization to access both databases will be managed and overseen by the project manager and the principal investigator. The Department of Biostatistics will maintain all de-identified data, cleaning and preparing the datasets for analysis.

Confidentiality will be maintained by assigning each participant a unique identification number and using this number to identify the participant on all data collection forms. We will keep all paper documents locked in lockable cabinets in a locked office suite. Most of the data will be entered directly into REDCap or Qualtrics, HIPAA-aligned web environments. Processes and procedures have been documented and implemented to ensure the security and protection of the data within the computer operations centers, the servers, and the databases. Only those study team members who need access to this information will be allowed by the PI or study coordinator. All participants will be fully informed about the study prior to enrollment and be given the opportunity to decline to answer any questions or to discuss any issues they find troubling. They will be told that they can terminate participation at any time for any reason.

Research team members will be trained in procedures to allow participant to withdraw from the study. REDCap and Qualtrics surveys will allow participants to pass over questions and still continue through the remainder of the questions.

All study team members including those involved with the recruitment, informed consent process, and data collection will be adequately trained. Training will include passing of our institution's required Collaborative Institutional Training Initiative (CITI) modules and ongoing study-specific training from study personnel.

Any files that contain protected health information that might be created during the course of the study will be stored on department servers. The PI and project manager will coordinate with the Department IT staff to control access to these folders.

In a step to minimize any confusion about the information presented to the patient-participants, all patients will initially view a video that provides information about CRC screening in an accessible and understanding way. It should be noted that patient responses to this type of video in previous research projects were great thankfulness for the information provided, which goes beyond what many patients hear from their doctor. In addition, since the participants will be recruited from a list of patients scheduled to receive care at the practice, they will have the chance to ask their health care provider for additional information. In fact, fostering such discussions is a potential benefit of study participation. In addition, the informed consent will give information on how to contact the principal investigator with any questions or concerns.

Protections for Research Data

Most of the data will be entered directly into one of several instruments in the study's REDCap project, a HIPAA aligned web environment. Privileges to the instruments will be granted or restricted by the PI or project manager based on what user rights are necessary to do the job. This could include no access, read only, or read and edit the data. Any files that contain protected health information that are created during the course of the study will be saved on the Department's servers. The PI or project manager will coordinate with the Department's IT to control access to these folders.

Protections for Participant Privacy

Initial contact with the patient will be a recruitment letter mailed through the US Postal Service to the address provided by the patient to be included in the EHR. The recruitment phone calls will be made from a private office to the phone number listed in the EHR and if additional phone calls are required, the recruiter will confirm with the potential participant their preferred contact number and time; the study team will make arrangements to comply with the potential participant's wishes.

Research staff will encourage the patient-participants to complete the baseline (T0) and post-intervention (T1) surveys and view the decision aid (intervention) in a quiet, private area; however, the participants ultimately will choose the location. Research Assistants will initially contact the participant to complete the post-visit survey (T2) and 6-month follow-up (T3) surveys by phone in a private office and conduct the interview at a time and phone number chosen by the participant. If the participant prefers to complete the surveys online, then the research assistant will email the participant the link to the surveys and the participant will choose where to complete the surveys.

Initial contact with the provider will also be with a recruitment letter delivered to their primary care practice by study team members. Providers will access the notification (intervention) using the procedures they usually would when they access any communication sent to them through their health systems' EHR. Providers will choose where they open their email and access the link to complete the provider surveys.

13.0 References

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14.0 Appendix

The appendix will be separate attachments for the Indiana University KC- IRB protocol (see Notes & Attachments in the KC-IRB protocol submission).