Impact of Patient Adherence to Stool-Based Colorectal Cancer Screening and Colonoscopy Following a Positive Test on Clinical Outcomes

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**ABSTRACT**

Colorectal cancer (CRC) screening models commonly assume 100% adherence, which is inconsistent with real-world experience. The influence of adherence to initial stool-based screening (fecal immunochemical test [FIT], multitarget stool DNA [mt-sDNA]) and follow-up colonoscopy (after a positive stool test) on CRC outcomes was modeled using CRC-AIM. Average-risk individuals without diagnosed CRC at age 40 undergoing annual FIT or triennial mt-sDNA screening from ages 50-75 were simulated. Primary analyses incorporated published mt-sDNA (71%) or FIT (43%) screening adherence, with follow-up colonoscopy adherence ranging from 40%-100%. Secondary analyses simulated 100% adherence for stool-based screening and colonoscopy follow-up (S1), published adherence for stool-based screening with 100% adherence to colonoscopy follow-up (S2) and published adherence for both stool-based screening and colonoscopy follow-up after positive mt-sDNA (73%) or FIT (47%) (S3). Outcomes were life-years gained (LYG) and CRC incidence and mortality reductions (per 1000 individuals) versus no screening. Adherence to colonoscopy follow-up after FIT had to be 4%-13% higher than mt-sDNA to reach equivalent LYG. The theoretical S1 favored FIT versus mt-sDNA (LYG 316 vs. 297; CRC incidence reduction 68% vs. 64%; CRC mortality reduction 76% vs. 72%). The more realistic S2 and S3 favored mt-sDNA versus FIT (S2: LYG 284 vs. 245, CRC incidence reduction 61% vs. 50%, CRC mortality reduction 69% vs. 59%; S3: LYG 203 vs. 113, CRC incidence reduction 43% vs. 23%, CRC mortality reduction 49% vs. 27%, respectively). Incorporating realistic adherence rates for CRC screening influences modeled outcomes and should be considered when assessing comparative effectiveness.

**Prevention Relevance Statement:** Adherence rates for initial CRC screening by FIT or mt-sDNA and for colonoscopy follow-up of a positive initial test influence the comparative effectiveness of these screening strategies. Using adherence rates based on published data for stool-based testing and colonoscopy follow-up yielded superior outcomes with an mt-sDNA versus FIT screening strategy.
Introduction

Screening for colorectal cancer (CRC) reduces CRC incidence and mortality by enabling
detection and treatment of adenomas and pre-symptomatic cancers. (1) Non-invasive stool
screening tests (including multitarget stool DNA [mt-sDNA] and fecal immunochemical test
[FIT]) are widely endorsed, but for screening to be complete a positive stool-test needs to be
followed by a colonoscopy. (1) Not surprisingly, in real-world settings, adherence to mt-sDNA
and FIT is reportedly imperfect. (2-5) In addition, the currently available published data suggest
that colonoscopy non-adherence following a positive non-invasive CRC screening test is
common and may differ between FIT and mt-sDNA. Within 6 months after a positive stool-test,
colonoscopy follow-up rates range from 43%-81% for FIT and 73%-96% for mt-sDNA. (6-11)
Non-adherence to colonoscopy follow-up undermines the achievable benefits of screening. One
study found that lack of colonoscopy follow-up after a positive stool-test increased the risk of
CRC by 1.83-fold and increased the risk of CRC-related death by 1.56-fold over a period of 6
years. (12) Delays in colonoscopy follow-up can also significantly increase the risk of incident
and fatal CRC. In a large retrospective study of patients with a positive stool-test, a ≥13 month
delay in follow-up colonoscopy increased the odds of CRC, and a ≥19 month delay increased the
odds CRC-related mortality when compared with a follow-up colonoscopy completed within 1-3
months. (13)

Microsimulation modeling of CRC screening strategies allows for estimating outcomes in an
average risk population under a variety of changeable assumptions. (14) CRC models have been
used to guide CRC screening recommendations. (15) However, many published modeling studies
incorporate a theoretical assumption of 100% patient adherence for all screening and follow-up
tests. The Colorectal Cancer and Adenoma Incidence and Mortality Microsimulation Model
(CRC-AIM) was previously used to comprehensively analyze the impact of adherence at
reported real-world adherence rates for stool-based testing, as well as outcomes over a full
spectrum of adherence ranging from 10% to 100% for each screening test, or assuming varying
numbers of completed stool-tests. (14) The results demonstrated that altering adherence rate
assumptions had a substantial impact on the predicted outcomes of CRC screening strategies and
shifted the order of model-recommend strategies to favor mt-sDNA over FIT. While the previous
analyses demonstrated the impact of initial screening adherence on predicted outcomes, the
influence of more realistic adherence to follow-up colonoscopy (when indicated) on achievable
screening outcomes remains incompletely defined. To build upon the impact of adherence to
CRC outcomes previously demonstrated using CRC-AIM, microsimulation analyses were
conducted to model the effects of (a) the traditional modeling approach of perfect adherence and
(b) reported adherence rates for FIT and mt-sDNA and colonoscopy follow-up for a positive
initial test on estimated life-years gained (LYG), CRC incidence, and CRC mortality.

Methods

The CRC-AIM model has been validated and full details are available elsewhere. (14, 16) CRC-
AIM incorporates assumptions related to the natural history of CRC and CRC screening and uses
these assumptions to calculate predicted outcomes in a simulated population. The natural history
component of CRC-AIM models the sequence of adenoma to carcinoma progression and
includes assumptions regarding the adenoma growth rate, adenoma location, adenoma to CRC transition probabilities, and growth of a CRC. The screening component incorporates assumptions about each CRC screening test’s sensitivity and specificity, as well as assumptions regarding complications and screening adherence.

For the present study, an average-risk US population birth cohort free of diagnosed CRC at age 40 that underwent triennial mt-sDNA or annual FIT screening from ages 50 to 75 was simulated using the CRC-AIM model. Primary analyses were performed using adherence published rates of 71% for initial mt-sDNA(2) and 43% for initial FIT(3, 4) screening, with colonoscopy follow-up adherence modeled across a wide range (40-100%). Patients without a colonoscopy follow-up were assumed to be non-adherent until CRC symptom onset.

Three adherence scenarios were further modeled in secondary analyses: Scenario 1 included the traditional assumption of 100% adherence for all stool-based screening and colonoscopy follow-up tests (best case); Scenario 2 included published adherence rates for initial mt-sDNA (71%)(2) or FIT (43%)(3, 4) screening, with assumed 100% adherence to colonoscopy follow-up; and Scenario 3 included published adherence rates for initial mt-sDNA(2) or FIT(3, 4) screening and published adherence rates for colonoscopy follow-up after positive mt-sDNA (73%) or FIT (47%).(6)

The predicted outcomes of LYG and percent reductions in CRC-related incidence and mortality in the simulated population were calculated for those undergoing a screening strategy (e.g., triennial mt-sDNA or annual FIT) and compared with those who were not screened. The outcome of LYG is defined as the number of LYG from screening that delayed or prevented death due to CRC. Outcomes for each scenario are reported per 1000 individuals.

Sensitivity analyses were further performed using a different published adherence rate for initial FIT screening of 48.2% observed in a retrospective cohort study and was within the context of an organized screening program.(5)

Results

With published adherence for stool screening-tests, over the range of adherence rates for colonoscopy follow-up, mt-sDNA achieved more LYG than FIT (Figure 1). Adherence to colonoscopy follow-up after FIT had to be 4% to 13% higher than mt-sDNA to reach equivalent LYG (Figure 1), 6% to 17% higher to reach equivalent reductions in CRC incidence, and 4% to 14% higher to reach equivalent reductions in CRC mortality.

In secondary analyses, the theoretical scenario 1 yielded better outcomes with FIT versus mt-sDNA (LYG 316 vs. 297; CRC incidence reduction 68% vs. 64%; CRC mortality reduction 76% vs. 72%), whereas the more realistic scenario 2 and scenario 3 favored mt-sDNA vs. FIT (Scenario 2: LYG 284 vs. 245, CRC incidence reduction 61% vs. 50%, CRC mortality reduction 69% vs. 59%; Scenario 3: LYG 203 vs. 113, CRC incidence reduction 43% vs. 23%, CRC mortality reduction 49% vs. 27%, respectively)(Figure 2). Each scenario yielded LYG and reductions in CRC incidence and CRC mortality with either mt-sDNA or FIT screening compared with no CRC screening (Figure 2).

The results in the sensitivity analysis were similar to the primary results (Figures 1 and 3).

Discussion
When published initial screening and colonoscopy follow-up adherence rates are used instead of assuming 100% adherence, the predicted benefits of the CRC screening process are substantially decreased. When adherence rates are modeled under a wide range of likely real-world scenarios, mt-sDNA yields greater CRC screening benefits than FIT. Furthermore, the overall results from the analysis support the concept that even under less than ideal adherence conditions, any CRC screening is beneficial and “the best test is the one that gets done.”

Stool-based CRC screening is not complete until a follow-up colonoscopy is performed after a positive stool-test. However, there are many reasons patients do not undergo a colonoscopy follow-up. Other health issues may be of higher priority or may not permit a colonoscopy to be safely performed. Often the patients simply refuse the colonoscopy follow-up. Fear or anxiety about the procedure and lack of belief or awareness in the importance are key reasons for refusal. Non-adherence to colonoscopy follow-up has also been shown to be driven by provider and system barriers. Some of these barriers include failure to inform the patient of a positive stool-test, failure to order the colonoscopy or a preprocedural evaluation, communication challenges, and lack of action by the gastroenterology clinic staff after the colonoscopy was ordered. CRC system-level navigation programs that track stool-test positive patients and contact patients by telephone to schedule appointments may increase the adherence to colonoscopy follow-up.

The currently reported analyses are limited by availability of existing data referent to real-world initial CRC screening and follow-up colonoscopy adherence rates. More research is needed to understand why the initial adherence is higher for mt-sDNA than FIT screening. However, a likely reason is the embedded patient reminders and patient navigation programs associated with all mt-sDNA test orders. Patient navigation has been shown to increase screening adherence and adherence rates of approximately 50% for FIT in the US have been observed in the context of a healthcare setting that included patient navigation. The published adherence rates may not be generalizable to all populations eligible for screening. For example, reported rates from a Medicare population, or from an integrated healthcare organization, or another socioeconomic or ethnic population may not extrapolate accurately to other age ranges, payers, and clinical settings. A broad range (43%-81%) of colonoscopy follow-up adherence 6 months after a positive FIT has been reported in the literature, depending on the evaluated population. Fewer studies have evaluated colonoscopy follow-up adherence after a positive mt-sDNA, with reported rates of 73% and 96% (we chose to apply the more conservative rate in our modeling). The higher adherence following positive mt-sDNA screening may be due to patient and/or provider perceptions regarding the utility of molecularly-driven screening represented by this assay approach. To account for potential variability in the colonoscopy follow-up adherence, the analysis used a range of 40% to 100% adherence. Given the uncertainty around the adherence rates, a sensitivity analysis using an initial FIT adherence of 48.2% was conducted and had little impact on the results.

Although adherence is a large driver of the difference in comparative effectiveness between mt-sDNA and FIT in the current analysis, and increasing FIT adherence may mitigate much of the benefit, differences in the tests themselves also contribute to differences in the predicted outcomes. For example, mt-sDNA has a higher sensitivity to detect CRC than FIT (92% vs 74%, respectively). A previous CRC-AIM analysis demonstrated that when assuming patients...
were randomly adherent to the same number of mt-sDNA and FIT tests, an individual would have to take up to 21 FIT tests to match the equivalent LYG as an individual who took up to 9 mt-sDNA tests.(14)

These findings demonstrate that incorporating realistic, rather than theoretical, adherence rates for initial stool screening and colonoscopy follow-up provides more clinically applicable outcomes data to inform further discussions referent to the comparative effectiveness of mt-sDNA- versus FIT-based strategies in real-world settings. Choice of test and comprehensive navigation support can favorably impact patient initiation and follow-through, affording great potential to enhance the overall effectiveness of CRC screening when regularly considered in program planning and evaluation.

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References


Figure Legends

**Figure 1.** Equal predicted life years-gained (LYG) for triennial multitarget stool DNA (mt-sDNA) and annual fecal immunochemical test (FIT) by the follow-up colonoscopy adherence rate. Circles indicate equivalent LYG when adherence to initial mt-sDNA and FIT screening is assumed to be 71% and 43%, respectively. Squares indicate equivalent LYG when adherence to initial mt-sDNA and FIT screening is assumed to be 71% and 48.2%, respectively (sensitivity analysis).

**Figure 2.** A) Predicted life years-gained (LYG), B) CRC incidence and mortality reduction for triennial multitarget stool DNA (mt-sDNA) and annual fecal immunochemical test (FIT) in 3 different adherence scenarios. Results are per 1000 individuals free of diagnosed colorectal cancer at age 40 and screened between 50–75 years. S1, 100% screening adherence and 100% colonoscopy follow-up adherence; S2, reported screening adherence and 100% colonoscopy follow-up adherence; S3, reported screening adherence and reported colonoscopy follow-up adherence.

**Figure 3.** Sensitivity analysis. A) Predicted life years-gained (LYG), B) CRC incidence and mortality reduction for triennial multitarget stool DNA (mt-sDNA) and annual fecal immunochemical test (FIT) in 3 different adherence scenarios. Results are per 1000 individuals free of diagnosed colorectal cancer at age 40 and screened between 50–75 years. S1, 100% screening adherence and 100% colonoscopy follow-up adherence; S2, sensitivity analysis rates for reported screening adherence and 100% colonoscopy follow-up adherence; S3, sensitivity analysis rates for reported screening adherence and reported colonoscopy follow-up adherence.
Figure 2.

A) Predicted life-years gained

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A) Predicted life-years gained

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