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*Ann Intern Med.* 2018 October 02; 169(7): 439–447. doi:10.7326/M18-0244.**Influence of varying quantitative fecal immunochemical test positivity thresholds on colorectal cancer detection: a community-based cohort study****Kevin Selby, MD<sup>1,2</sup>, Christopher D. Jensen, PhD<sup>1</sup>, Jeffrey K. Lee, MD, MAS<sup>1</sup>, Chyke A. Doubeni, MD, MPH<sup>3</sup>, Joanne E. Schottinger, MD<sup>4</sup>, Wei K. Zhao, MPH<sup>1</sup>, Jessica Chubak, PhD<sup>5</sup>, Ethan Halm, MD, MPH<sup>6</sup>, Nirupa R. Ghai, PhD<sup>7</sup>, Richard Contreras, MS<sup>4</sup>, Celette Skinner, PhD<sup>6</sup>, Aruna Kamineni, PhD<sup>5</sup>, Theodore R. Levin, MD<sup>8</sup>, and Douglas A. Corley, MD, PhD<sup>1</sup>**

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**Abstract**

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**Author Contributions:** Dr Selby had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data: Data set can be available for collaborative efforts by contacting Dr. Douglas Corley at [douglas.corley@kp.org](mailto:douglas.corley@kp.org).

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**Background:** The fecal immunochemical test (FIT) is commonly used for colorectal cancer (CRC) screening. Despite demographic variations in stool hemoglobin concentrations, little data exist regarding optimal positivity thresholds by age and sex.

**Objective:** Identify programmatic (multi-test) FIT performance characteristics and optimal FIT quantitative hemoglobin positivity thresholds in a large, population-based screening program.

**Design:** Retrospective cohort study

**Setting:** Kaiser Permanente Northern and Southern California

**Participants:** Adults 50–75 years of age, screening eligible, with baseline quantitative FIT results (2013–2014), and 2 years follow-up. Nearly two-thirds (411,641) had a previous FIT within 2 years.

**Measurements:** FIT programmatic sensitivity for CRC and number of positive tests per cancer detected, overall and by age and sex.

**Results:** Among 640,859 persons completing a baseline FIT and followed for 2 years, 481,817 (75%) had 1 additional FIT and 1,245 (0.19%) were diagnosed with CRC. Cancer detection (programmatic sensitivity) increased at lower positivity thresholds, from 925/1,245 (74.3%) at 30  $\mu\text{g/g}$ , to 950 (76.3%) at 20  $\mu\text{g/g}$ , and 987 (79.3%) at 10  $\mu\text{g/g}$ ; the number of positive tests per cancer detected increased from 43 at 30  $\mu\text{g/g}$ , to 52 at 20  $\mu\text{g/g}$ , and 85 at 10  $\mu\text{g/g}$ . Reducing the positivity threshold from 20 to 15  $\mu\text{g/g}$  would detect 3% more cancers and require 23% more colonoscopies. At the conventional 20  $\mu\text{g/g}$  FIT threshold, programmatic sensitivity decreased with increasing age (79.0%, 73.4%, and 68.9% for ages 50–59, 60–69 and 70–75 years, respectively,  $p=0.009$ ) and was higher in men than women (77.0% vs. 70.6%,  $p=0.011$ ).

**Limitations:** Information on advanced adenoma were lacking.

**Conclusion:** Increased cancer detection at lower positivity thresholds is counter-balanced by substantial increases in positive tests. Tailored thresholds may provide more comparable screening benefits for different demographic groups, dependent upon local resources.

## Keywords

colorectal cancer; screening; fecal occult blood tests; sensitivity and specificity; number needed to scope

## Introduction:

Colorectal cancer (CRC) is the second-leading cause of cancer mortality in the United States (US)(1). Screening with guaiac-based fecal occult blood tests reduced CRC mortality in randomized trials by 15 to 33% (2, 3). The fecal immunochemical test (FIT) has several advantages over guaiac-based tests, including greater specificity for human hemoglobin, the need for only a single fecal sample, and no requirement for dietary or medication restrictions (1, 4).

Quantitative FITs directly measure human hemoglobin concentrations in the stool. The quantitative threshold for a positive FIT result (positivity threshold) can be tailored to different settings and patient groups to optimize cancer detection (sensitivity), while limiting

the number of colonoscopies triggered by positive FIT results. Population-based screening programs worldwide use a broad range of FIT positivity thresholds, ranging from 10 to 47  $\mu\text{g}$  hemoglobin/g (5), although 20  $\mu\text{g}$ /g is the convention in the US (6). Few comparisons between positivity thresholds exist from screening programs in large diverse populations (7, 8). Furthermore, there are differences in fecal hemoglobin concentrations between population groups, with reports of higher concentrations in men than women and increasing concentrations with age (9–11). Likewise, CRC incidence is higher in men than women, and increases with age (12). In contrast, women have a higher incidence of proximal cancers (right sided) that may be more difficult to detect by screening (13, 14). Consequently, utilizing the same FIT positivity threshold across subgroups may be suboptimal (15). Previous studies examining positivity thresholds have been limited by an insufficient number of cancer diagnoses needed to define the sensitivity of FIT, particularly in demographic subgroups (4, 7, 14, 16–18), were conducted with population samples that did not resemble the general US population (19), used outdated or qualitative tests (4), or lacked comprehensive follow-up of negative FIT results needed to identify missed CRCs (i.e., false negatives)(20, 21).

We examined FIT screening performance measures in two large, community-based, screening programs using mailed FIT outreach with linkage to comprehensive cancer registries. We assessed the balance of cancer detection and screening burden at varying FIT positivity thresholds. Our goal was to quantify the programmatic sensitivity of FIT (over multiple rounds of testing) and the potential impact of various positivity thresholds on a screening program, in a cohort representative of a community-based, diverse population.

## Methods

### Study Setting:

This retrospective cohort study included members of Kaiser Permanente Northern California (KPNC) and Southern California (KPSC) who completed FIT screening between January 1, 2013 and December 31, 2014. KPNC and KPSC are integrated healthcare systems with approximately 8 million members receiving care across 40 medical centers. These systems provide comprehensive care, an integrated electronic health record, and cancer registries reporting to the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) program. Their diverse membership closely approximates the adult census population in California, except at extremes of income (22–24). The study was approved by the institutional review boards of KPNC and KPSC, and was conducted within the National Cancer Institute-funded Population-based Research to Optimize the Screening Process (PROSPR II) consortium, which conducts multisite, coordinated, transdisciplinary research to evaluate and improve cancer screening processes.

### Fecal immunochemical tests:

KPNC and KPSC have organized FIT-based CRC screening outreach programs that began between 2006 and 2008 (8, 25). Members 50–75 years of age without a colonoscopy within 10 years or sigmoidoscopy within 5 years were mailed a FIT kit annually. The kit included a one-sample FIT (OC FIT-CHEK; Polymedco), a standardized letter, directions for

completing the test, and a preprinted laboratory requisition form. Patients mailed their completed FIT to a regional laboratory, where it was analyzed using an OC-Sensor Diana automated system (Polymedco) with the threshold for a positive test of  $>20 \mu\text{g/g}$  (corresponding to 100 nanograms of hemoglobin/ml of test buffer) (26). Patients with a result at the threshold were classified as negative. Patients with positive results were referred for colonoscopy. Patients and providers were informed if the result was “positive” or “negative”, but were not provided with the actual quantitative values. Tests with a value  $>200 \mu\text{g/g}$  were read as “over assay” and reported as positive.

### Overall cohort eligibility criteria and follow-up:

Individuals were eligible if they had a quantitative FIT result available between January 1, 2013 and December 31, 2014, irrespective of whether it was their first-ever FIT; were 50–75 years of age; were at average risk for CRC (no personal history of CRC, total colectomy, or inflammatory bowel disease); and had been members of the health system for 2 years before the test result date (to capture prior endoscopy examinations or FIT). Patients were followed for 2 years after the test result date or until their CRC diagnosis date if it was within 2 years.

### Data sources:

Quantitative FIT values were obtained directly from the automated OC-Sensor Diana machine. Patient characteristics (date of birth, sex, body mass index (BMI), race and Hispanic ethnicity) were obtained from the electronic health record. The number of primary care visits and Charlson comorbidity scores were computed with a standardized algorithm using *International Classification of Diseases, Ninth Revision* codes from care episodes in the calendar year before the baseline FIT (27). Colorectal adenocarcinoma diagnoses were obtained from the KPNC and KPSC cancer registries, which capture greater than 99% of cancers diagnosed among members, compared with manual review, and include the cancer site, morphology, and stage. Cancers were diagnosed in three main ways: by colonoscopy done for follow-up of positive FIT; by colonoscopy or radiologic imaging exams done after negative FIT because of symptoms or laboratory abnormalities (e.g. anemia); and by colonoscopy after negative FIT because subsequent to the FIT, the patient elected to continue future screening with an elective colonoscopy. We only considered adenocarcinomas, which represent approximately 90–95% of all CRCs, because these tumors are believed to follow the adenoma-carcinoma sequence and are potentially preventable through screening (28, 29). Cancer location was defined as the right colon (proximal to the splenic flexure), left colon, or rectum. Advanced-stage cancers were defined as stage III (regional lymph node involvement) or stage IV (distant metastasis) according to the American Joint Committee on Cancer staging system or as code 3 (disease in the regional lymph nodes), code 4 (regional disease with direct extension and spread to regional lymph nodes), or code 7 (distant metastasis) according to the 2013 SEER Program Coding and Staging Manual 2013 (30).

### Data Analysis:

The distribution of baseline quantitative FIT values among those with and without CRC during follow-up, by age and sex, were summarized using percentiles. The primary analysis

was the programmatic sensitivity, specificity, and corresponding confidence intervals at FIT positivity thresholds of 10, 15, 20, 25 and 30 µg/g. Programmatic sensitivity was the proportion of patients with a CRC diagnosis within 2 years of FIT screening who had a quantitative FIT result above a given positivity threshold at baseline or during follow-up testing; programmatic specificity was the proportion of patients without a CRC diagnosis with all quantitative FIT results at or below a given threshold. The number of cancers diagnosed and the number individuals with a positive test were calculated at each threshold. The number of participants with a positive test per cancer detected was calculated at each threshold. The same test characteristics were examined separately by age (50–59, 60–69 and 70–75 years) and sex (male and female), with comparisons between subgroups using the  $\chi^2$  and ANOVA tests. Analyses were repeated using only the baseline FIT result and 1 year of follow-up in the cancer registry to evaluate the impact of a single test using the recommended 1-year screening interval in the United States, and to limit the effect of repeated screening on results (4). Analyses used SAS Version 9.4 (SAS Institute) and Stata Version 14 (StataCorp).

### Role of Funding Sources:

The study was funded by the National Cancer Institute and the Swiss Cancer Research Foundation, neither of which had a role in the conception, design, analysis, or conduct of the study.

### Results:

#### Overall cohort Characteristics:

Of 1,550,542 members who received a FIT, 1,212,461 (78%) completed 1 FIT in 2013–2014 (Figure 1). A total of 640,859 patients (53%), including 401,975 at KPNC and 238,884 at KPSC, had 1 quantitative FIT result and met the inclusion criteria; 411,241 (64%) completed a previous FIT within 2 years of the baseline FIT (Table 1). During 2 years of follow-up, 159,042 (25%) did not complete additional FIT screening after the baseline, 250,519 (39%) completed 1 additional FIT, and 231,298 (36%) completed 2 additional FITs (Figure 1). A total of 48,561 (7.6%) patients had a positive result at the conventional positivity threshold of 20 µg/g, of whom 36,906 (76%) had a colonoscopy within 2 years of the baseline FIT (median 33 days after the result). The distributions of positive tests, colonoscopy follow-up, and cancer diagnoses were similar between those with quantitative results and the overall population of KPNC and KPSC members tested during the study period (data not shown).

Of 1,245 cancers diagnosed at or within 2 years of the baseline FIT, 505 (41%) were in the right colon, 358 (29%) in the left colon, 362 (29%) in the rectum, and 20 (1.6%) of undefined primary location (Table 1). The proportion of right-sided cancers increased with age (29% between 50–59 years, 44% between 60–69 years, and 53% between 70–75 years,  $p<0.001$ ), and was higher in women than men (46% vs. 36%,  $p=0.004$ ) (supplemental Tables 1 and 2). Among those who did not develop cancer during follow-up, baseline stool hemoglobin values at the 95th percentile increased with age (13.4 µg/g for age 50–59, 16.2 µg/g for age 60–69, and 21.0 µg/g for age 70–75,  $p<0.001$ ), and were higher in men than

women (17.8 µg/g vs. 13.4 µg/g,  $p<0.001$ )(Supplemental table 3). For those who developed cancer, median stool hemoglobin values from the baseline FIT were higher for left-sided than right-sided cancers or rectal cancers (60.0 µg/g, 12.4 µg/g, and 24.4 µg/g respectively,  $p<0.001$  for each 2-way comparison)(Supplemental table 3).

#### **FIT performance at varying positivity thresholds in the overall cohort:**

The proportion of cancers detected by FIT (programmatic sensitivity) decreased with higher positivity thresholds, from 987 of 1,245 cancers at 10 µg/g (79.3%), to 925 at 20 µg/g (74.3%), and 822 at 30 µg/g (66.0%) (Table 3). The number of participants with a positive baseline or subsequent FIT test also decreased, from 84,293 at 10 µg/g (13.2% with positive test, programmatic specificity 87.0%), to 48,561 at 20 µg/g (7.6% with positive test, specificity 92.6%), and 35,017 at 30 µg/g (5.5% with positive test, specificity 96.8%).

The number of positive tests per cancer detected increased substantially at thresholds below 20 µg/g. Positive tests per cancer detected increased 11% from 25 to 20 µg/g (47 to 52), 22% from 20 to 15 µg/g (52 to 63), and 35% from 15 to 10 µg/g (63 to 85). Reducing the positivity threshold from 20 to 15 µg/g would have detected 25 additional cancers (3% increase) from 11,308 additional colonoscopies (23% increase), equating to 452 colonoscopies per additional cancer detected.

#### **FIT performance at varying positivity thresholds stratified by age:**

Programmatic sensitivity and specificity decreased significantly with increasing age at thresholds between 10 and 30 µg/g. At 20 µg/g, the programmatic sensitivity decreased from 79.0% (95%CI 74.8–82.7) among those 50–59 years, to 73.4% among those 60–69 years (95%CI 69.4–77.1), and 68.9% among those 70–75 years (95%CI 63.2–74.3,  $p=0.009$ ) (Table 4). Programmatic specificity declined with age, from 93.5% (95%CI 93.4–93.6) among those 50–59 years, to 90.6% (95%CI 90.4–90.8) among those 70–75 years ( $p<0.001$ ), as the number of positive tests per cancer detected decreased from 63 (57–70) to 40 (35–47).

#### **FIT performance at varying positivity thresholds stratified by sex:**

At all thresholds between 10 and 30 µg/g, FIT had lower programmatic sensitivity and higher programmatic specificity among women than men (Table 4). At 20 µg/g, the programmatic sensitivities were 77.0% (95%CI 73.7–80.0) and 70.6% (95%CI 66.6–74.5) for men and women respectively ( $p=0.011$ ), and the programmatic specificities were 91.6% (95%CI 91.5–91.7) and 93.4% (95%CI 93.3–93.5) ( $p<0.001$ ). Decreasing the threshold from 20 to 10 µg/g led to substantial increases in the number of positive tests per cancer detected for both sexes, increasing 62% from 47 (95%CI 43–51) to 76 (95%CI 70–83) in men, and 63% in women from 60 (95%CI 55–67) to 98 (95%CI 89–108). Decreasing the threshold for women from 20 to 10 µg/g yielded a programmatic sensitivity similar to that of men at the 20 µg/g threshold, but with a lower programmatic specificity (88.2% vs. 91.6%) and more than double the number of positive results per cancer detected (98 vs. 47).

### Additional analyses with 1-year follow-up:

Similar patterns were seen for the trade-off of sensitivity and specificity, both overall and among subgroups, using only 1-year of follow-up from the baseline FIT result (Supplementary Materials). FIT sensitivity of the baseline test only with 1-year of follow-up was slightly higher (77.7% at 20 µg/g (95% CI 72.6–81.0)) compared to the programmatic sensitivity with 2 years of follow-up (74.3% (95% CI 71.8–76.7)); FIT specificity was also higher (95.9% (95% CI 95.9–96.0) vs. a programmatic specificity of 92.6% (95% CI 92.5–92.6) (Supplemental Table 6).

### Discussion:

In this large, diverse, community-based sample of adults participating in FIT screening, programmatic sensitivity for CRC increased modestly with decreasing positivity thresholds, from 74.3% at 20 µg/g, to 76.3% at 15 µg/g, and 79.3% at 10 µg/g. The number of positive tests per cancer detected over 2 years increased with decreasing positivity thresholds, especially below 20 µg/g. FIT performance varied by age and sex, with lower programmatic sensitivity and specificity with increasing age, and higher programmatic sensitivity and lower specificity in men than women.

The 5% point increase in CRC programmatic sensitivity observed when decreasing the positivity threshold from 20 to 10 µg/g is smaller than differences reported in some prior studies (31), although prior reports have been inconsistent and had small numbers of cancers, resulting in low precision (wide confidence intervals) (32–34). A systematic review of several FIT brands found that a threshold of <20 µg/g yielded an overall sensitivity of 86% (95% CI 75–92) vs. 63% (95% CI 43–79) for thresholds between 20–50 µg/g (4). Previous studies with colonoscopy follow-up of all screening participants have compared FIT sensitivity (using OC-Sensor Diana) for advanced adenomas at varying thresholds (32–35). They have shown 5–10% increases in advanced adenoma sensitivity when decreasing the positivity threshold from 20 to 10 µg/g. This increase is larger than we observed for cancers, and is clinically relevant given that approximately 25% of advanced adenomas will progress to CRC over 10 years (36).

A few prior studies with colonoscopy follow-up suggested that FIT sensitivity for CRC and advanced adenomas is higher and specificity lower in men than women (10, 34, 37), though reports are conflicting and did not allow precise estimates by quantitative FIT thresholds (19). Proposed explanations for this disparity include a higher proportion of harder-to-detect, right-sided cancers (34), lower serum hemoglobin concentrations (10), and longer colonic transit times in women than in men (38). Women in our cohort had a higher proportion of right-sided cancers than men, and women with cancer had lower mean stool hemoglobin concentrations than men with cancer (Supplemental table 3). Women also had smaller relative reductions in CRC mortality than men in previous randomized trials of guaiac tests (39). The apparent lower sensitivity of FIT in women is concerning given that sigmoidoscopy also appears less effective in women (40). There are few published reports of FIT performance trends by age, though FIT may perform better below age 50 than above (41), and worse above age 65 (42).

Our findings suggest that screening programs wishing to increase cancer detection by lowering their positivity threshold below the conventional 20 µg/g will require substantial additional colonoscopy and financial resources. The large increases in the number of positive tests per cancer detected are likely because CRC is rare in screening populations and more overlap in lower fecal hemoglobin concentrations between those with and without CRC. Some additional colonoscopies generated by positive tests without a cancer (false positives in this study) would detect and remove advanced adenomas, likely reducing future cancer incidence (8, 31). However, repeat annual testing can mean larger accumulated numbers of false positive tests; our 2-year programmatic specificity results were substantially lower than one-time test specificity with 1-year follow-up (supplementary materials). The optimal positivity threshold (acceptable number of positive tests per cancer detected) will depend on the availability of local colonoscopy resources. Lower resourced settings may raise their positivity threshold, although in our study sensitivity at 30 µg/g declined from 74.3% to 66.0%. Notably, a screening program in the Netherlands increased their threshold from 15 to 47 µg/g following unexpectedly high colonoscopy demand (43).

The implications for screening programs of the observed differences in programmatic sensitivity and specificity by age and sex are less clear, and likely depend on the relative importance given to colonoscopy burden or maximizing cancer detection across subgroups. As might be expected, given the lower baseline fecal hemoglobin concentrations in women, we observed a larger increase in programmatic sensitivity when decreasing the positivity threshold from 20 to 10 µg/g in women than in men (7.1% vs. 3.5% increase), although women also had a larger increase in the number of positive tests per cancer (38 vs. 29 more tests), likely due to their lower cancer incidence rates. Lowering the positivity threshold for women may achieve comparable sensitivity to men and fewer interval cancers (34, 44), although others have proposed more aggressive screening in men due to their higher risk (12, 45, 46). We are not aware of previous work advocating lower positivity thresholds in older age groups. While FIT programmatic sensitivity and the number of positive tests per cancer detected were lowest in those aged 70–75 years, both the risk of cancer and the risk of complications from colonoscopy increase with age (1).

Strengths of our study include a diverse, multi-center community-based screening cohort, with quantitative FIT results available, including from repeated testing; analyses from multiple laboratories; high overall screening rates, decreasing the potential for selection bias (47); high-quality cancer registries; more cancers than previous studies (7, 16–18); and a US screening population (19, 32).

Our study also has several potential limitations. First, we did not have quantitative FIT values available on all members who underwent FIT screening during the study interval. However, analyses by season and medical center did not reveal any pattern in missing quantitative values, and our positive predictive values were similar to previous publications from the entire population, including those without quantitative values (8, 48). Second, we assumed all cancers with quantitative values  $\geq 20$  µg/g would be detected if designated positive; although follow-up colonoscopy rates and cancer registry ascertainment are high in the KPNC and KPSC screening programs (49), imperfect follow-up would likely attenuate the benefit of lowering the positivity threshold. Third, despite cancer registry follow-up,



estimates of programmatic sensitivity incorporate some differential verification bias: patients with a FIT result  $>20$   $\mu\text{g/g}$  were likely to receive immediate, invasive ascertainment sensitive for early-stage CRC (colonoscopy), rather than clinical follow-up with less sensitive ascertainment (cancer registry). Differential verification bias falsely increases sensitivity in studies of 1-time fecal-based cancer screening because of incomplete accrual of false negatives (50), and could make the current threshold of 20  $\mu\text{g/g}$  appear more advantageous. However, our primary results focus on the performance of a screening program over 2 years rather than a single FIT. Fourth, we could not measure false negatives for advanced adenomas and thus our findings may reflect only part of the benefit of lower positivity thresholds. However, smaller studies have been able to estimate the effect of varying positivity thresholds on advanced adenoma detection using the same FIT brand (OC-Sensor Diana) (32–35). Fifth, because participants were followed for two calendar years and not precisely two rounds of screening, there may not have been sufficient time for colonoscopy follow-up of positive tests occurring towards the end of the 2-year follow-up. Finally, most participants had prior FIT screening, which, by removing some prevalent cancers, may have increased the number of positive tests per cancer detected as compared to screening naïve populations (8). However, as screening programs mature, it is important to measure test performance in heterogeneous populations of first-time and repeat screenees.

## Conclusions

Among participants in a FIT-based screening program followed for 2 years from their baseline FIT, cancer detection and the number of positive tests per cancer detected varied significantly and substantially by age and sex, suggesting that modifications in positivity thresholds by subgroups could optimize screening program performance, although also with impacts on the number of false-positive tests. Modifying the positivity threshold for the overall study population from the current US conventional value of 20 to 15  $\mu\text{g/g}$  would have resulted in 25 additional cancers detected (3% increase), and required the evaluation of 11,308 additional positive tests (23% increase). Further research is needed to assess the cost-effectiveness of such changes and practicality across settings with differing resources.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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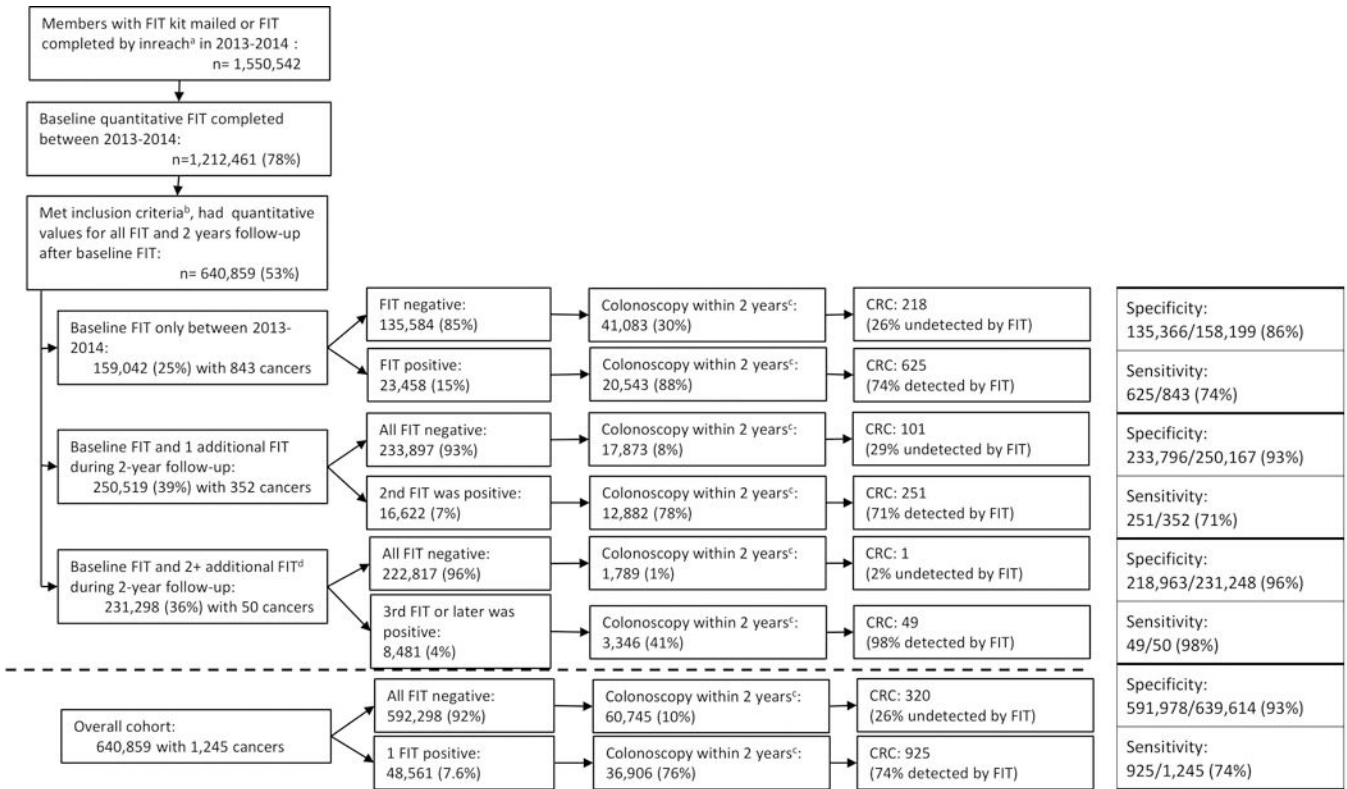
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**Figure 1:** Number of fecal immunochemical tests (FIT) completed, FIT results, number of colonoscopies, and cancer diagnoses among patients with 1 FIT completed in 2013–2014 and followed for 2 years from their baseline FIT. <sup>a</sup>Inreach is the local distribution of FIT by primary care staff or otherwise. <sup>b</sup>Inclusion criteria: 50–75 years of age; 2 years Kaiser Permanente membership prior to baseline FIT; no prior diagnosis of inflammatory bowel disease or CRC; no prior colectomy; and quantitative values available for all FITs during 2-year study interval. Patients followed for 2 years after the baseline FIT. <sup>c</sup>2-year time interval started at time of the baseline FIT. Overall, 80% of patients received a colonoscopy within 180 days of a positive FIT. <sup>d</sup>226,984 completed 2 additional FIT, 4,161 completed 3 additional FIT, and 153 completed 4 additional FIT during the 2-year follow-up. FIT: fecal immunochemical test, CRC: colorectal cancer

**Table 1:**

Patient characteristics and colorectal cancer outcomes within 2 years of a baseline fecal immunochemical test (FIT) among participants who completed 1 FIT (n=640,859)

<b>Participant Characteristics</b>	
Female sex	337,588 (53%)
Age at time of FIT	
50 to 59 years	323,855 (51%)
60 to 69 years	234,665 (37%)
70 to 75 years	82,339 (13%)
Race/ethnicity	
Non-Hispanic white	352,913 (55%)
Hispanic	114,724 (18%)
Black	46,925 (7%)
Asian/Pacific islander	103,958 (16%)
Other or unknown	22,339 (3%)
Obese (BMI $\geq 30$ kg/m <sup>2</sup> ) <sup>a</sup>	215,312 (34%)
Primary care visits in year preceding test	
No primary care visit	124,285 (19%)
1 to 3 primary care visits	367,406 (57%)
4 or more primary care visits	149,168 (23%)
Charlson comorbidity score year prior to baseline FIT	
Score = 0	443,577 (69%)
Score = 1 or 2	153,825 (24%)
Score = 3	43,457 (7%)
Previous FIT within 2 years of baseline FIT	
Yes	411,241 (64%)
No	229,618 (36%)
<b>Outcomes during follow-up</b>	
Colonoscopy within 2 years	97,651 (15%)
Baseline FIT > 20 $\mu$ g/g	26,654 (4.2%)
Colorectal cancer diagnosed within 2 years of baseline FIT	1,245 (0.19%)
Right-sided colon cancer	505 (41%)
Left-sided colon cancer	358 (29%)
Rectal cancer	362 (29%)
Location unknown	20 (2%)
Colorectal cancer stage at diagnosis	
Early	1,064 (85%)
Late	181 (15%)

<sup>a</sup>Body mass index (BMI) was missing for 15,360 patients (2%). FIT: fecal immunochemical test

Colorectal cancer (CRC) detection within 2 years of a baseline fecal immunochemical test (FIT) at various positivity thresholds

Table 2:

Overall cohort (n=640,859)	Threshold for test positivity				
	30 µg/g	25 µg/g	20 µg/g <sup>d</sup>	15 µg/g	10 µg/g
Cancers detected	822/1,245	867/1,245	925/1,245	950/1,245	987/1,245
Programmatic sensitivity <sup>b</sup> (95% CI)	66.0% (63.3–68.7)	69.6% (67.0–72.2)	74.3% (71.8–76.7)	76.3% (73.8–78.6)	79.3% (76.9–81.5)
Programmatic specificity <sup>c</sup> (95% CI)	94.7% (94.6–94.7)	93.8% (93.8–93.9)	92.6% (92.5–92.6)	90.8% (90.7–90.9)	87.0% (86.9–87.1)
Positive FIT at baseline or within 2 years <sup>d</sup>	35,017 (5.5%)	40,399 (6.3%)	48,561 (7.6%)	59,869 (9.3%)	84,293 (13.2%)
Positive results / 1 cancer detected (95% CI)	43 (40–46)	47 (44–50)	52 (49–56)	63 (59–67)	85 (80–91)

<sup>a</sup>The current United States conventional FIT positivity threshold is 20 µg/g

<sup>b</sup> Among those with colorectal cancer, the proportion with a positive FIT at baseline or within 2 years

<sup>c</sup> Among those without cancer, the proportion without a positive FIT at baseline or within 2 years

<sup>d</sup> Individuals with a positive result at baseline or within 2 years



Colorectal cancer (CRC) detection within 2 years of a baseline fecal immunochemical test (FIT) at various positivity thresholds by an organized outreach program using annual FIT, stratified by age and sex.

**Table 3:**

	Threshold for FIT positivity:				
	30 µg/g	25 µg/g	20 µg/g <sup>d</sup>	15 µg/g	10 µg/g
<b>Age 50–59 years (n=323,855)</b>					
Cancers detected	298/428	315/428	338/428	342/428	354/428
Programmatic sensitivity <sup>b</sup> (95% CI)	69.6% (65.0–74.0)	73.6% (69.2–77.7)	79.0% (74.8–82.7)	79.9% (72.6–81.0)	82.7% (78.8–86.2)
Programmatic specificity <sup>c</sup> (95% CI)	95.3% (95.2–95.3)	94.6% (94.5–94.6)	93.5% (93.4–93.6)	92.0% (91.9–92.1)	88.7% (88.6–88.8)
Positive FIT at baseline or within 2 years <sup>d</sup>	15,605 (4.8%)	17,878 (5.5%)	21,321 (6.6%)	26,230 (8.1%)	36,892 (11%)
Positive results / 1 cancer (95% CI)	52 (47 – 59)	57 (51 – 64)	63 (57 – 70)	76 (69 – 85)	104 (94 – 116)
<b>Age 60–69 years (n=234,665)</b>					
Cancers detected	353/534	370/534	392/534	403/534	421/534
Programmatic sensitivity <sup>b</sup> (95% CI)	66.1% (61.9–70.1)	69.3% (65.2–73.2)	73.4% (69.4–77.1)	75.5% (71.6–79.1)	78.8% (75.1–82.2)
Programmatic specificity <sup>c</sup> (95% CI)	94.3% (94.2–94.4)	93.3% (93.2–93.4)	91.9% (91.8–92.0)	90.0% (89.8–90.1)	85.7% (85.6–85.9)
Positive FIT at baseline or within 2 years <sup>d</sup>	13,745 (5.9%)	15,955 (6.8%)	19,355 (8.3%)	23,897 (10%)	33,847 (14%)
Positive results / 1 cancer (95% CI)	39 (35 – 43)	43 (39 – 48)	49 (45 – 55)	59 (54 – 65)	80 (73 – 89)
<b>Age 70–75 years (n=82,056)</b>					
Cancers detected	171/283	182/283	195/283	205/283	212/283
Programmatic sensitivity <sup>b</sup> (95% CI)	60.4% (54.5–66.2)	64.3% (58.4–69.9)	68.9% (63.2–74.3)	72.4% (66.8–77.6)	74.9% (69.4–79.9)
Programmatic specificity <sup>c</sup> (95% CI)	93.3% (93.1–93.5)	92.2% (92.0–92.4)	90.6% (90.4–90.8)	88.4% (88.2–88.6)	83.7% (83.5–84.0)
Positive FIT at baseline or within 2 years <sup>d</sup>	5,667 (6.9%)	6,566 (8.0%)	7,885 (9.6%)	9,742 (12%)	13,554 (16%)
Positive results / 1 cancer (95% CI)	33 (29 – 39)	36 (31 – 42)	40 (35 – 47)	48 (42 – 55)	64 (56 – 73)
<b>Men (n=303,271)</b>					
Cancers detected	489/717	517/717	552/717	562/717	577/717
Programmatic sensitivity <sup>b</sup> (95% CI)	68.2% (64.7–71.6)	72.1% (68.7–75.4)	77.0% (73.7–80.0)	78.4% (75.2–81.3)	80.5% (77.4–83.3)

	Threshold for FIT positivity:				
	30 µg/g	25 µg/g	20 µg/g <sup>d</sup>	15 µg/g	10 µg/g
Programmatic specificity <sup>c</sup> (95% CI)	93.9% (93.8–94.0)	93.0% (92.9–93.1)	91.6% (91.5–91.7)	89.7% (89.6–89.8)	85.6% (85.5–85.7)
Positive FIT at baseline or within 2 years <sup>d</sup>	18,899 (3.8%)	21,654 (7.1%)	25,932 (8.6%)	31,814 (11%)	44,108 (15%)
Positive results / 1 cancer (95% CI)	39 (35–42)	42 (39–42)	47 (43–51)	57 (52–62)	76 (70–83)
<b>Women (n=429,590)</b>					
Cancers detected	333/528	350/528	373/528	388/528	410/528
Programmatic sensitivity <sup>b</sup> (95% CI)	63.1% (58.8–67.2)	66.3% (62.1–70.3)	70.6% (66.6–74.5)	73.5% (69.5–77.2)	77.7% (73.9–81.1)
Programmatic specificity <sup>c</sup> (95% CI)	95.3% (95.2–95.4)	94.5% (94.5–94.6)	93.4% (93.3–93.5)	91.8% (91.7–91.9)	88.2% (88.1–88.3)
Positive FIT at baseline or within 2 years <sup>d</sup>	16,118 (4.8%)	18,745 (5.6%)	22,629 (6.7%)	28,055 (8.3%)	40,185 (12%)
Positive results / 1 cancer (95% CI)	48 (44–54)	54 (48–60)	60 (55–67)	72 (66–80)	98 (89–108)

<sup>a</sup>The current United States conventional FIT positivity threshold is 20 µg/g

<sup>b</sup>Among those with colorectal cancer, the proportion with a positive FIT at baseline or within 2 years

<sup>c</sup>Among those without cancer, the proportion without a positive FIT at baseline or within 2 years

<sup>d</sup>Individuals with a positive FIT at baseline or within 2 years