

Colorectal Cancer Screening at Younger Ages: A Multicutoff Analysis of FIT Performance

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Abstract

Fecal immunochemical tests (FIT) are established for colorectal cancer (CRC) screening, but performance data in younger adults remains limited. Using screening colonoscopy data from 1705 participants, we assessed FIT performance and sex differences. Sensitivity and specificity matched older populations, yet many advanced neoplasia occurred in the upper negative range, underscoring potential for improved, risk-adapted early CRC screening.

Background: Due to rising early-onset colorectal cancer (CRC) incidence, lowering the starting age for CRC screening is considered in many countries. However, data on diagnostic performance of fecal immunochemical tests (FIT), the most commonly employed CRC screening test, in younger populations remain limited. This study assessed FIT diagnostic performance for detecting advanced neoplasia (AN) at various cutoffs of fecal hemoglobin (Hb) concentrations in individuals aged 55 years or younger. **Methods:** A total of 1724 participants aged 55 years or younger who underwent screening colonoscopy were recruited in a cross-sectional study conducted in Germany. Fecal Hb concentrations were measured in all participants using FIT (Sentinel FOB Gold) prior to colonoscopy. AN prevalence was determined by screening colonoscopy. FIT performance was evaluated based on positivity rate, sensitivity, specificity, and predictive values at various Hb concentration thresholds. **Results:** AN was detected in 139 participants (8.1%), including 5 participants (0.3%) with CRC. At the manufacturer-recommended cut off of 17 µg Hb/g stool, positivity rate was 7.7%, yielding a sensitivity of 26.6% (95% confidence interval [CI], 20.0-34.5), specificity of 94.0% (95% CI, 92.7-95.1), positive predictive value (PPV) of 28.0% (95% CI, 21.1-36.2), and negative predictive value (NPV) of 93.6% (95% CI, 92.3-94.7) for AN detection. These measures strongly varied across the range of cutoffs employed in FIT-based screening programs. Men showed higher AN prevalence, positivity rate, sensitivity, and PPV across the investigated Hb range, whereas sex differences in specificity and NPV were minimal. **Conclusion:** Our study provides detailed quantitative information on diagnostic performance characteristics of FIT in a younger CRC screening population, which may inform and optimize effectiveness and cost-efficiency of CRC screening at younger ages.

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Keywords: Advanced neoplasia, CRC, Early-onset CRC, Test performance, FIT, Screening

Background

Fecal immunochemical tests (FITs) are the most widely used tests for colorectal cancer (CRC) screening.^{1,2} They are commonly

used as dichotomous tests, in that screening participants with fecal hemoglobin (Hb) concentrations above a defined threshold are referred to colonoscopy, or otherwise to continue with annual or biennial FIT screening. Many screening programs simply adopted the positivity threshold recommended by the manufacturer,³⁻⁶ whereas others adapted the threshold to higher values due to limited colonoscopy capacities.⁷ However, the definition of the positivity threshold may have major implications on diagnostic performance parameters, such as sensitivity, specificity, and positive and negative predictive values (PPV, NPV), all of which are crucial for the effectiveness and cost-effectiveness of CRC screening. Knowledge of FIT performance parameters according to positivity threshold is therefore crucial for designing and offering FIT-based screening in the most effective and cost-effective manner.

Abbreviations: AN, advanced colorectal neoplasia; CRC, colorectal cancer; FIT, fecal immunochemical test; Hb, Hemoglobin; NPV, negative predictive value; PPV, positive predictive value.

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Data on diagnostic performance of FIT in real-life screening settings is increasingly available from FIT-based organized screening programs. These programs enable quantification of positive predictive values for CRC and its precursors for the specific positivity threshold employed in the program from the results of the colonoscopies following positive FITs.⁸⁻¹¹ Along with quantitative FIT results, these colonoscopy results also enable quantification of PPVs for potential alternative, higher FIT cutoffs. However, PPVs for lower FIT positivity thresholds or absolute values of sensitivity and specificity for any positivity threshold cannot be determined from such programs due to the lack of colonoscopies among participants below the program's specific positivity threshold.

The evidence base for diagnostic performance of FITs is even more limited for CRC screening at younger ages,¹²⁻¹⁴ which has become of increasing interest and relevance due to a concerning rise in CRC incidence at prescreening ages that has been observed in recent years in many countries.^{15,16} The aim of this study was to provide a comprehensive evaluation of key diagnostic performance parameters of a quantitative FIT in a German cohort of screening participants who underwent screening colonoscopy as a primary screening exam below the age of 55.

Methods

Study Population

Study participants were recruited between 2008 and 2020 as part of the BLITZ (Begleitende Evaluierung innovativer Testverfahren zur Darmkrebs-Früherkennung) study, an ongoing study among participants of screening colonoscopy, which has been offered as a primary screening examination in Germany since 2002. Most screening colonoscopies were performed in the outpatient setting under strict rules of quality control by certified gastroenterologists. The BLITZ study is conducted by the German Cancer Research Center in cooperation with gastroenterology practices in southern Germany. More detailed information on the BLITZ study has been reported previously.¹⁷ The study protocol is registered with the German Clinical Trials Register (DRKS00008737). The study was approved by the ethics committee of the Heidelberg University (178/2005), the State Chamber of Physicians of Baden-Wuerttemberg (M118-05-f), Saarland (217/13), Rhineland-Palatinate (837.047.06(5145)), and Hesse (MC 254/2007). Informed written consent was obtained from all study participants.

Sample and Data Collection

Participants completed a standardized questionnaire that inquired about their sociodemographic background and lifestyle habits. Colonoscopy and pathology report data were extracted independently by 2 trained research assistants who were blinded to questionnaire responses and FIT results. Colonoscopy results were categorized according to the most advanced findings: CRC, advanced adenoma, sessile serrated polyp ≥ 1 cm, nonadvanced adenoma, other, or no finding. Adenomas with at least one of the following features were defined as advanced: ≥ 1 cm in size, tubulovillous or villous components, or high-grade dysplasia. Participants having advanced adenomas or sessile serrated polyps ≥ 1 cm as the most advanced finding were classified as having advanced precancerous

lesions (APCL). For analytical purposes, we defined the primary outcome as advanced neoplasia (AN), which encompassed both CRC and APCL.

Stool collection and sampling have previously been described in detail elsewhere.¹⁸ In short, stool samples were collected prior to bowel preparation for subsequent colonoscopy without any dietary restrictions. During the recruitment period for this analysis, the same quantitative FIT (FOB Gold, Sentinel Diagnostics, Milan, Italy) was applied. Stool samples collected between 2008 and 2012 were collected in specimen containers and frozen until delivery to the laboratory. Stool samples collected after 2012 were collected directly in FIT tubes and sent in for Hb measurements. Both methods were previously shown to yield comparable results.¹⁹ Samples were analyzed at an external laboratory (Labor Limbach, Heidelberg, Germany) by trained personnel, blinded to colonoscopy results, on the Abbott Architect c8000 (Abbott Diagnostics, Abbott Park, IL). Median time from sample collection to analysis was 3 days (interquartile range: 2-5 days). Measured fecal Hb concentrations (ng Hb/mL Buffer) were converted to μg Hb/g stool before analysis to ensure comparability among studies.²⁰

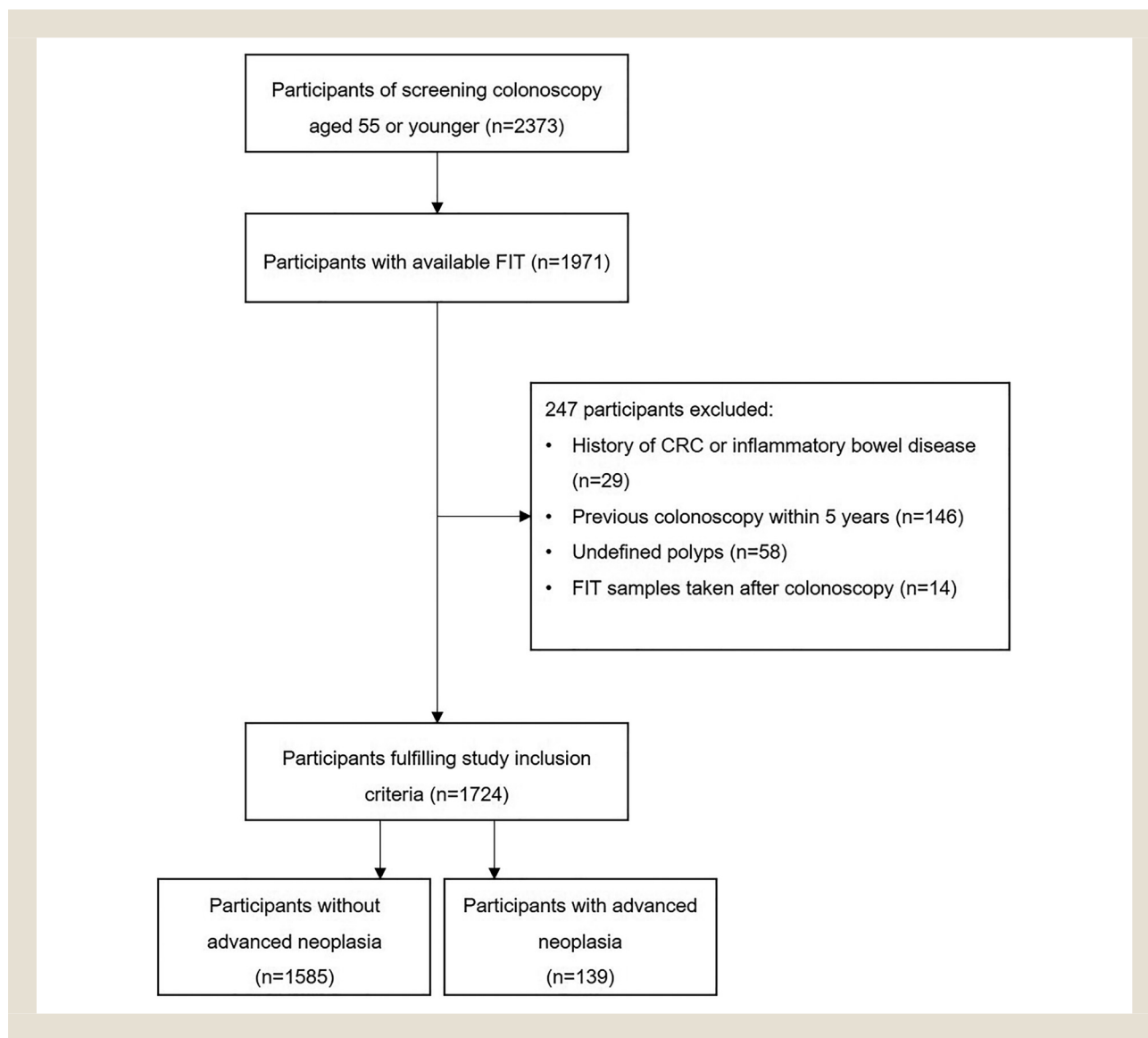
Statistical Analysis

We included participants aged 55 years and younger for all subsequent analyses. Prevalence and distribution of AN were determined within different concentration ranges of fecal Hb, both in the entire study population and separately for men and women. Sensitivity, specificity, PPVs and NPVs, along with corresponding 95% confidence intervals (CI), were calculated for several cutoffs of measured fecal Hb concentrations (2, 4, 6, 8, 9, 10, 12, 17, 20, 30, 50, and 100 $\mu\text{g/g}$). Diagnostic discrimination of fecal Hb measured by FIT was assessed using receiver operating characteristic analysis, and the area under the curve (AUC) with the corresponding 95% CI was calculated. Exploratory associations of sociodemographic and lifestyle factors with FIT positivity (≥ 17 μg Hb/g stool) were performed, whose results are presented as crude prevalence ratios and 95% CIs. All statistical analyses were performed using R software v. 4.1.2 (R Foundation for Statistical Computing).

Results

Of 2373 study participants aged 55 years or younger, 1971 had available FIT results (Figure 1). A total of 247 individuals were excluded due to a history of CRC or inflammatory bowel disease ($n = 29$), previous colonoscopy within 5 years ($n = 146$), undefined polyps ($n = 58$), or FIT sample submission after colonoscopy ($n = 14$), resulting in 1724 eligible participants. Among the 1724 participants, slightly more than half were women (51.2%, $n = 882$). The mean age was 52.5 years, with most participants (79.6%) being between 51 and 55 years of age, whereas 20.5% were 50 years or younger. Overall, 139 participants (8.1%) were diagnosed with AN. Mean fecal Hb levels were considerably higher among participants with advanced colorectal neoplasia (Table 1).

Table 2 shows the distribution of measured fecal Hb levels across the study population and corresponding prevalences of advanced colorectal neoplasia determined by colonoscopy. In this cohort, Hb concentrations remained below the limit of detection (1.7 $\mu\text{g/g}$) in 678 participants (39.3%). Overall, 88.5% ($n = 1525$) of partic-

Figure 1 Flow chart of participant selection.

Participants demonstrated fecal Hb levels lower than 10 µg/g, while fewer than 3% (n = 43) exceeded 100 µg/g. Among all individuals, 133 (7.7%) had concentrations above 17 µg/g, their results would be considered positive based on the cutoff recommended by the manufacturer. Notably, the prevalence of AN increased with rising fecal Hb levels, showing a marked increase in AN prevalence for Hb concentrations already in the upper range of negative FIT results (between 8 and 17 µg/g). Observed prevalence of AN was higher among men (n = 85) compared to women (n = 54), whereas the distribution of measured Hb concentrations was comparable.

Different metrics of diagnostic performance at selected FIT cutoffs for the presence of advanced colorectal neoplasia are shown in Table 3. At the manufacturer-recommended threshold of 17 µg/g stool the positivity rate was 7.7%, with a sensitivity of 26.6% (95% CI, 20.0-34.5), specificity of 94.0% (95% CI, 92.7-95.1),

a PPV of 28.0% (95% CI, 21.1-36.2), and a NPV of 93.6% (95% CI, 92.3-94.7). As the fecal Hb concentration cutoff was incrementally increased from 2 to 100 µg/g, the percentage of positive tests decreased substantially, dropping from 59.4% to 2.4%. This change was accompanied by a reduction in sensitivity, which declined from 69.8% (95% CI, 61.7-76.8) to 12.2% (95% CI, 7.8-18.7). Conversely, the specificity of the test improved substantially, rising from 41.5% (95% CI, 39.1-44.0) to 98.4% (95% CI, 97.7-98.9) at the highest threshold. Parallel to these changes, the PPV rose from 9.5% (95% CI, 7.8-11.4) at the lowest threshold to 40.5% (95% CI, 27.0-55.5) at the highest. The NPV remained relatively stable across the range of cutoffs, only slightly decreasing from 94.0% (95% CI, 92.0-95.5) to 92.7% (95% CI, 91.4-93.9). When compared to the default threshold, lowering the threshold to 10 µg/g increased sensitivity by 8.7 percentage points, with specificity decreasing by only 3.4 points. Further reductions to 9 or

Table 1 Study Population Characteristics

Variable		Total (N = 1724)	No AN (N = 1585)	AN (N = 139)
Sex	Women	882 (51.2%)	828 (52.2%)	54 (38.8%)
	Men	840 (48.7%)	755 (47.6%)	85 (61.2%)
	Missing	2 (0.1%)	2 (0.1%)	0 (0%)
Age	Mean (SD)	52.5 (4.26)	52.5 (4.32)	52.8 (3.58)
	Median (Min, Max)	55.0 (22.0, 55.0)	55.0 (22.0, 55.0)	54.0 (32.0, 55.0)
Age categories	≤45 years	113 (6.6%)	106 (6.7%)	7 (5.0%)
	46–≤50 years	239 (13.9%)	225 (14.2%)	14 (10.1%)
	51–≤55 years	1372 (79.6%)	1254 (79.1%)	118 (84.9%)
Concentration of fecal hemoglobin by FIT	Mean (SD)	8.64 (24.5)	6.89 (19.2)	28.6 (52.9)
	Median (Min, Max)	3.23 (0, 333)	3.06 (0, 292)	5.61 (0, 333)
Most advanced finding at	Colorectal cancer	5 (0.3%)		5 (3.6%)
	Advanced adenoma	134 (7.8%)		134 (96.4%)
	Nonadvanced adenoma	291 (16.9%)	291 (18.4%)	
	Hyperplastic polyp	175 (10.1%)	175 (11.0%)	
	No finding	1119 (64.9%)	1119 (70.6%)	

Abbreviations: AN = advanced neoplasia; FIT = fecal immunochemical tests; min = minimum; max = maximum; SD = standard deviation.

8 µg/g increased sensitivity by 12.2 and 13.7 points, respectively, while specificity dropped by 5.1 and 6.8 points.

At the positivity threshold recommended by the manufacturer, we observed a higher positivity rate (8.4% vs. 6.9%), sensitivity (29.4% vs. 22.2%), and PPV (35.2% vs. 19.7%) among men than among women. By contrast, specificity was very similar in both sexes, and the NPV was higher in women than in men (94.9% vs. 92.2%). Throughout the range of evaluated thresholds over 4 µg/g, men consistently showed a higher positivity rate, sensitivity, and PPV compared to women (Table 4). Conversely, women exhibited slightly higher NPVs for most thresholds. Continuous performance metrics stratified by sex are displayed in Supplemental Figure 1. Fecal Hb concentration showed an AUC of 0.637 (95% CI, 0.582–0.692) for the detection of AN (Supplemental Figure 2). Exploratory associations between participant characteristics and FIT positivity are presented in Supplemental Table 1.

Discussion

In this study, we provide a comprehensive assessment of fecal Hb concentrations and their association with detection of advanced colorectal neoplasia in an average-risk screening population aged 55 years or younger. We further assessed sensitivity, specificity, and predictive values for fecal Hb levels in association with presence of advanced colorectal neoplasia at a variety of thresholds. We observed higher prevalence of AN with rising Hb concentrations and a strong increase in prevalence of AN well below the manufacturer-recommended cutoff (17 µg/g), ie, between Hb levels of 8 and 17 µg/g. Furthermore, we observed a higher prevalence of AN among men along with higher sensitivity and PPV across the investigated range of Hb, whereas sex differences in specificity and NPV remained small.

In recent decades, the epidemiological landscape of CRC has shifted, with a notable decrease in incidence among older populations in countries with successfully implemented screening programs, contrasting with an emerging rise in younger cohorts.¹⁶ Nevertheless, in absolute terms, the incidence in younger individuals remains low.²¹ Therefore, the applicability and, consequently, the benefit of extending current screening protocols, which were primarily designed for older individuals, to younger age groups requires careful evaluation. Among potential screening tests for younger ages, FIT appears to be a particularly appealing option due to its noninvasive nature and the low per-test costs.²²

Our study extends previous research by evaluating diagnostic performance of FIT for detection of AN at multiple thresholds in a cohort aged 55 years or younger. Cutoff-specific sensitivities and specificities in our study closely mirrored those previously reported for older participants of screening colonoscopy in Germany,²³ suggesting broadly comparable diagnostic discrimination in the present study population. Moreover, we observed, in line with previous studies including older age groups, a considerably increased prevalence of AN already in the upper range of FIT-negative results (8–17 µg/g) compared to lower range values²³ and larger tradeoffs for sensitivity and specificity for very low thresholds.^{24–26} Our results suggest that sex-specific differences in FIT performance, previously reported in older cohorts,^{27–29} are also present among adults aged 55 years or younger. Whether and to what extent such sex differences may warrant sex-specific screening recommendations would need to be evaluated in further research, including comprehensive cost-effectiveness analyses, for which our results may provide valuable input data.

While using FITs as dichotomous tests with fixed, uniform cutoffs offer practical advantages for large-scale screening programs, our results suggest that the use of quantitative information from FIT

Table 2 Prevalence of Advanced Neoplasia According to Fecal Hemoglobin Concentrations for All Participants and Stratified by Sex

Test Result	Fecal Hemoglobin (µg/g)	All Participants				Men				Women			
		Total		AN		Total		AN		Total		AN	
		N = 1724	col %	N = 139	Prevalence % (95% CI)	N = 840	col %	N = 85	Prevalence % (95% CI)	N = 882	col %	N = 54	Prevalence % (95% CI)
Negative ^a	<1.7	678	39.3	42	6 (4-8)	315	37.5	26	8 (5-11)	363	41.2	16	4 (2-7)
	1.7-<8	787	45.6	41	5 (4-7)	381	45.4	24	6 (4-9)	404	45.8	17	4 (2-6)
	8-<17	126	7.3	19	15 (9-21)	73	8.7	10	14 (6-22)	53	6.0	9	17 (7-27)
Positive ^a (n = 133)	17-<50	63	3.7	11	17 (8-27)	28	3.3	5	18 (4-32)	35	4.0	6	17 (5-30)
	>50	70	4.1	26	37 (26-48)	43	5.1	20	47 (32-61)	27	3.1	6	22 (7-38)

Alternative categorization

	<1.7	678	39.3	42	6 (4-8)	315	37.5	26	8 (5-11)	363	41.2	16	4 (2-7)
	1.7-<5	462	26.8	22	5 (3-7)	231	27.5	12	5 (2-8)	230	26.1	10	4 (2-7)
	5-<10	385	22.3	26	7 (4-9)	181	21.5	14	8 (4-12)	203	23	12	6 (3-9)
	10-<20	78	4.5	15	19 (10-28)	48	5.7	9	19 (8-30)	30	3.4	6	20 (6-34)
	20-<50	51	3.0	8	16 (6-26)	22	2.6	4	18 (2-34)	29	3.3	4	14 (1-26)
	50-<100	27	1.6	8	30 (12-47)	19	2.3	7	37 (15-59)	8	0.9	1	13 (0-35)
	>100	43	2.5	18	42 (27-57)	24	2.9	13	54 (34-74)	19	2.2	5	26 (7-46)

Abbreviations: AN = advanced neoplasia; CI = confidence interval; col% = column percentage.

^a Test cutoff (17 µg Hb/g stool) recommended by the manufacturer (Sentinel Diagnostics, Milano, Italy).

Table 3 Diagnostic Performance Measures for FIT Performance at Various Fecal Hemoglobin Concentration Thresholds

Cutoff µg/g	Positivity (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
2	59.4	69.8 (61.7-76.8)	41.5 (39.1-44.0)	9.5 (7.8-11.4)	94.0 (92.0-95.5)
4	43.5	61.2 (52.9-68.8)	58.0 (55.6-60.5)	11.3 (9.3-13.8)	94.5 (92.8-95.7)
6	24.2	44.6 (36.6-52.9)	77.5 (75.4-79.5)	14.8 (11.7-18.6)	94.1 (92.7-95.3)
8	15.0	40.3 (32.5-48.6)	87.2 (85.5-88.7)	21.6 (17.0-27.0)	94.3 (93.0-95.4)
9	13.3	38.8 (31.2-47.1)	88.9 (87.3-90.3)	23.5 (18.5-29.4)	94.3 (93.0-95.4)
10	11.5	35.3 (27.8-43.5)	90.6 (89.1-91.9)	24.7 (19.3-31.2)	94.1 (92.8-95.2)
12	9.8	32.4 (25.2-40.5)	92.2 (90.8-93.4)	26.6 (20.5-33.8)	94.0 (92.7-95.0)
17 ^a	7.7	26.6 (20.0-34.5)	94.0 (92.7-95.1)	28.0 (21.1-36.2)	93.6 (92.3-94.7)
20	7.0	24.5 (18.1-32.2)	94.5 (93.3-95.5)	28.1 (20.9-36.7)	93.4 (92.1-94.6)
30	5.5	20.9 (14.9-28.4)	95.9 (94.8-96.8)	30.9 (22.4-40.8)	93.3 (91.9-94.4)
50	4.1	18.7 (13.1-26.0)	97.2 (96.3-97.9)	37.1 (26.8-48.9)	93.2 (91.8-94.3)
100	2.4	12.2 (7.8-18.7)	98.4 (97.7-98.9)	40.5 (27.0-55.5)	92.7 (91.4-93.9)

Abbreviations: CI = confidence interval; FIT = fecal immunochemical tests; NPV = negative predictive value; PPV = positive predictive value.

^a Test cutoff recommended by the manufacturer (Sentinel Diagnostics, Milano, Italy).

Table 4 Diagnostic Performance Measures for FIT Performance at Various Fecal Hemoglobin Concentration Thresholds, Stratified by Sex

	Cutoff µg/g	Positivity (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Women						
	2	57.5	70.4 (57.2-80.9)	43.2 (39.9-46.6)	7.5 (5.5-10.1)	95.7 (93.2-97.3)
	4	43.1	61.1 (47.8-73.0)	58.0 (54.6-61.3)	8.7 (6.2-11.9)	95.8 (93.7-97.2)
	6	22.9	42.6 (30.3-55.8)	78.4 (75.5-81.1)	11.4 (7.7-16.5)	95.4 (93.6-96.8)
	8	13.0	38.9 (27.0-52.2)	88.6 (86.3-90.6)	18.3 (12.3-26.3)	95.7 (94.0-96.9)
	9	11.5	37.0 (25.4-50.4)	90.1 (87.9-91.9)	19.6 (13.1-28.4)	95.6 (94.0-96.9)
	10	9.7	29.6 (19.1-42.8)	91.5 (89.5-93.3)	18.6 (11.8-28.1)	95.2 (93.5-96.5)
	12	8.5	25.9 (16.1-38.9)	92.6 (90.6-94.2)	18.7 (11.5-28.9)	95.0 (93.3-96.3)
	17 ^a	6.9	22.2 (13.2-34.9)	94.1 (92.3-95.5)	19.7 (11.6-31.3)	94.9 (93.2-96.2)
	20	6.3	18.5 (10.4-30.8)	94.4 (92.7-95.8)	17.9 (10.0-29.8)	94.7 (92.9-96.0)
	30	4.2	13.0 (6.4-24.4)	96.4 (94.9-97.5)	18.9 (9.5-34.2)	94.4 (92.7-95.8)
	50	3.1	11.1 (5.2-22.2)	97.5 (96.2-98.3)	22.2 (10.6-40.8)	94.4 (92.6-95.7)
	100	2.1	9.3 (4.0-19.9)	98.3 (97.2-99.0)	26.3 (11.8-48.8)	94.3 (92.6-95.7)
Men						
	2	61.0	69.4 (59.0-78.2)	39.7 (36.3-43.3)	11.5 (9.0-14.5)	92.0 (88.6-94.5)
	4	43.6	61.2 (50.5-70.8)	58.3 (54.7-61.7)	14.2 (11.0-18.1)	93.0 (90.4-95.0)
	6	25.7	45.9 (35.7-56.4)	76.6 (73.4-79.4)	18.1 (13.5-23.7)	92.6 (90.3-94.4)
	8	17.1	41.2 (31.3-51.8)	85.6 (82.9-87.9)	24.3 (18.0-31.9)	92.8 (90.7-94.5)
	9	15.2	40.0 (30.2-50.6)	87.5 (85.0-89.7)	26.6 (19.7-34.8)	92.8 (90.7-94.5)
	10	13.3	38.8 (29.2-49.5)	89.5 (87.1-91.5)	29.5 (21.8-38.5)	92.9 (90.8-94.5)
	12	11.2	36.5 (27.0-47.1)	91.7 (89.5-93.4)	33.0 (24.3-43.0)	92.8 (90.7-94.4)
	17 ^a	8.4	29.4 (20.8-39.8)	93.9 (92.0-95.4)	35.2 (25.1-46.8)	92.2 (90.1-93.9)
	20	7.7	28.2 (19.8-38.6)	94.6 (92.7-96.0)	36.9 (26.2-49.1)	92.1 (90.0-93.8)
	30	6.8	25.9 (17.8-36.1)	95.4 (93.6-96.6)	38.6 (27.1-51.6)	92.0 (89.8-93.7)
	50	5.1	23.5 (15.8-33.6)	97.0 (95.5-98.0)	46.5 (32.5-61.1)	91.8 (89.7-93.5)
	100	2.7	14.1 (8.3-23.1)	98.5 (97.4-99.2)	52.2 (33.0-70.8)	91.1 (88.9-92.8)

Abbreviations: CI = confidence interval; FIT = fecal immunochemical tests; NPV = negative predictive value; PPV = positive predictive value.

^a Test cutoff recommended by the manufacturer (Sentinel Diagnostics, Milano, Italy).

measurements may enable more refined, personalized screening approaches. For example, our results suggest that individuals aged 55 years and younger with higher “negative” Hb levels, who exhibit substantially increased likelihood of advanced colorectal neoplasia compared to those with low levels, may benefit from shorter screening intervals. By contrast, screening intervals might potentially be prolonged among the vast majority of participants with very low fecal Hb concentrations, which may help to reduce unnecessary colonoscopies through lowering false positive rates and save colonoscopy resources for those at higher risk.

Our study offers several notable strengths. First, it is one of the few studies in which all participants, ie, both FIT-positive and FIT-negative participants, underwent colonoscopy, which allowed evaluation of absolute values of diagnostic performance across the entire range of fecal Hb concentrations. Second, by calculating performance estimates across a range of FIT cutoffs rather than relying on a single threshold, our study offers a more comprehensive view of the sensitivity-specificity tradeoffs, supporting the identification of optimal screening thresholds in different screening contexts. Finally, we examined sex-specific differences, providing insights into potential disparities in FIT performance between men and women within this age group. Despite these advantages, the study also has some important limitations. Despite the overall large sample size and number of cases with AN, the number of CRC cases in this young screening population was too small to derive reliable estimates of diagnostic performance parameters for this outcome. Furthermore, although our study population was restricted to screening participants up to 55 years of age, the number of participants below age 50 was rather small, which limited possibilities to conduct more detailed age-specific analyses. The use of one FIT brand restricts the generalizability of our findings to other FIT manufacturers, as test performance may vary among different manufacturers.^{17,29,30} Moreover, as most participants were aged 50 to 55 years, the precision and generalizability of our findings are greatest for this age group, whereas evidence for substantially younger adults remains more limited. Our predominantly white study population limits the applicability of the results to more diverse groups. Finally, our cross-sectional design precludes assessment of long-term outcomes, such as progression from early to advanced lesions over time.

Conclusion

Despite its limitations, our study provides valuable insights into the performance of FIT for detecting advanced colorectal neoplasia in younger populations. Notably, cutoff-specific sensitivity and specificity estimates in individuals aged 55 years and younger closely mirrored those reported for established screening-age cohorts, suggesting broadly comparable diagnostic discrimination in the study population. In particular, in agreement with previous findings for screening participants at older ages, our results indicate substantially increased prevalence of AN already below the standard FIT cutoff, ie, in the “upper negative range” of FIT values, which suggests potential to further refine FIT-based screening strategies, eg, by risk-adapted screening intervals. Although our results offer a comprehensive assessment of FIT performance across various thresholds, further research is needed to validate these findings in diverse populations and to evaluate long-term outcomes. As the

incidence of early-onset colorectal cancer continues to rise, refining screening strategies for younger adults becomes increasingly important. Our study may provide a reference and inform future decisions for personalized screening approaches.

Clinical Practice Point

- Fecal immunochemical tests (FIT) are widely used for colorectal cancer (CRC) screening, offering non-invasive, cost-effective detection of advanced colorectal neoplasia. However, despite the rising incidence of early-onset CRC, data on FIT performance in younger populations remain limited.
- In a cohort of 1,705 individuals aged ≤ 55 years undergoing screening colonoscopy, FIT showed sensitivity and specificity comparable to previously reported levels from older screening populations. However, a notable proportion of advanced neoplasia occurred within the upper range of FIT-negative results, suggesting a potential for enhanced sensitivity by lowering established FIT cutoffs, or for use of quantitative FIT results for enhanced, risk-adapted screening intervals.
- Our study provides detailed quantitative information on diagnostic performance characteristics of FIT in a younger CRC screening population. Adaptation of FIT cutoffs enables tailoring FIT based screening at younger ages to available colonoscopy capacities and to optimize effectiveness and cost-effectiveness of screening for early-onset colorectal cancer.

Data Transparency Statement

Data used in this study are available from the corresponding author on reasonable request.

Disclosures

The authors have stated that they have no conflicts of interest.

CRedit authorship contribution statement

Julia Hibbert: Writing – original draft, Software, Formal analysis. **Teresa Seum:** Writing – review & editing, Project administration. **Michael Hoffmeister:** Writing – review & editing, Supervision, Methodology. **Hermann Brenner:** Writing – original draft, Supervision, Methodology, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.clcc.2026.07.001](https://doi.org/10.1016/j.clcc.2026.07.001).

References

- Ola I, Cardoso R, Hoffmeister M, Brenner H. Utilization of colorectal cancer screening tests across European countries: a cross-sectional analysis of the European health interview survey 2018-2020. *Lancet Reg Health Eur*. 2024;41:100920. doi:10.1016/j.lanepe.2024.100920.
- Ola I, Cardoso R, Hoffmeister M, Brenner H. Utilization of colorectal cancer screening tests: a systematic review and time trend analysis of nationally representative data. *EClinicalMedicine*. 2024;75:102783. doi:10.1016/j.eclinm.2024.102783.
- Plantener E, Deding U, Madsen JB, Kroijer R, Madsen JS, Baatrup G. Using fecal immunochemical test values below conventional cut-off to individualize colorectal cancer screening. *Endosc Int Open*. 2022;10(4):E413–e419. doi:10.1055/a-1743-2651.
- Zorzi M, Urso EDL. Impact of colorectal cancer screening on incidence, mortality and surgery rates: evidences from programs based on the fecal immunochemical test in Italy. *Digest Liver Dis*. 2023;55(3):336–341. doi:10.1016/j.dld.2022.08.013.
- Wang Y-W, Chen H-H, Wu M-S, Chiu H-M. Current status and future challenge of population-based organized colorectal cancer screening: lesson from the first decade of Taiwanese program. *J Formosan Med Assoc*. 2018;117(5):358–364. doi:10.1016/j.jfma.2017.09.010.
- Saito Y, Oka S, Kawamura T, et al. Colonoscopy screening and surveillance guidelines. *Dig Endosc*. 2021;33(4):486–519. doi:10.1111/den.13972.
- Toes-Zoutendijk E, van Leerdam ME, Dekker E, et al. Real-time monitoring of results during first year of Dutch colorectal cancer screening program and optimization by altering fecal immunochemical test cut-off levels. *Gastroenterology*. 2017;152(4):767–775.e2. doi:10.1053/j.gastro.2016.11.022.
- Auge JM, Pellise M, Escudero JM, et al. Risk stratification for advanced colorectal neoplasia according to fecal hemoglobin concentration in a colorectal cancer screening program. *Gastroenterology*. 2014;147(3):628–636.e1. doi:10.1053/j.gastro.2014.06.008.
- Njor SH, Andersen B, Friis-Hansen L, et al. The optimal cut-off value in fit-based colorectal cancer screening: an observational study. *Cancer Med*. 2021;10(5):1872–1879. doi:10.1002/cam4.3761.
- Sarkeala T, Färkkilä M, Anttila A, et al. Piloting gender-oriented colorectal cancer screening with a faecal immunochemical test: population-based registry study from Finland. *BMJ Open*. 2021;11(2):e046667. doi:10.1136/bmjopen-2020-046667.
- Westerberg M, Eriksson J, Metcalfe C, et al. Colonoscopy findings after increasing two-stool faecal immunochemical test (FIT) cut-off: cross-sectional analysis of the SCREESCO randomized trial. *J Intern Med*. 2024;296(2):187–199. doi:10.1111/joim.13810.
- Jung YS, Park CH, Kim NH, Park JH, Park DI, Sohn CI. Colorectal cancer screening with the fecal immunochemical test in persons aged 30 to 49 years: focusing on the age for commencing screening. *Gastrointest Endosc*. 2017;86(5):892–899. doi:10.1016/j.gie.2017.03.1531.
- Kim NH, Park JH, Park DI, Sohn CI, Choi K, Jung YS. The fecal immunochemical test has high accuracy for detecting advanced colorectal neoplasia before age 50. *Dig Liver Dis*. 2017;49(5):557–561. doi:10.1016/j.dld.2016.12.020.
- D'Souza N, Monahan K, Benton SC, Wilde L, Abulafi M. NICE FIT Steering Group. Finding the needle in the haystack: the diagnostic accuracy of the faecal immunochemical test for colorectal cancer in younger symptomatic patients. *Colorectal Dis*. 2021;23(10):2539–2549. doi:10.1111/codi.15786.
- Stoffel EM, Murphy CC. Epidemiology and mechanisms of the increasing incidence of colon and rectal cancers in young adults. *Gastroenterology*. 2019;158(2):341–353. doi:10.1053/j.gastro.2019.07.055.
- Sung H, Siegel RL, Laversanne M, et al. Colorectal cancer incidence trends in younger versus older adults: an analysis of population-based cancer registry data. *Lancet Oncol*. 2025;26(1):51–63. doi:10.1016/s1470-2045(24)00600-4.
- Gies A, Cuk K, Schrotz-King P, Brenner H. Direct comparison of diagnostic performance of 9 quantitative fecal immunochemical tests for colorectal cancer screening. *Gastroenterology*. 2018;154(1):93–104. doi:10.1053/j.gastro.2017.09.018.
- Niedermaier T, Guo F, Weigl K, Hoffmeister M, Brenner H. Combined performance of fecal immunochemical tests and a genetic risk score for advanced neoplasia detection. *Cancer Prev Res (Phila)*. 2022;15(8):543–552. doi:10.1158/1940-6207.Capr-21-0552.
- Chen H, Werner S, Brenner H. Fresh vs frozen samples and ambient temperature have little effect on detection of colorectal cancer or adenomas by a fecal immunochemical test in a colorectal cancer screening cohort in Germany. *Clin Gastroenterol Hepatol*. 2017;15(10):1547–1556.e5. doi:10.1016/j.cgh.2016.10.018.
- Fraser CG, Allison JE, Halloran SP, Young GP. A proposal to standardize reporting units for fecal immunochemical tests for hemoglobin. *J Natl Cancer Inst*. 2012;104(11):810–814. doi:10.1093/jnci/djs190.
- Kolb JM, Hu J, DeSanto K, et al. Early-age onset colorectal neoplasia in average-risk individuals undergoing screening colonoscopy: a systematic review and meta-analysis. *Gastroenterology*. 2021;161(4):1145–1155.e12. doi:10.1053/j.gastro.2021.06.006.
- Issaka RB, Avila P, Whitaker E, Bent S, Somsouk M. Population health interventions to improve colorectal cancer screening by fecal immunochemical tests: a systematic review. *Prev Med*. 2019;118:113–121. doi:10.1016/j.ypmed.2018.10.021.
- Niedermaier T, Heisser T, Cardoso R, Hoffmeister M, Brenner H. Colonoscopy-ascertained prevalence of advanced neoplasia according to fecal hemoglobin concentration in a large cohort of fecal immunochemical test-negative screening participants. *Ann Intern Med*. 2023;176(11):1569–1571. doi:10.7326/m23-1358.
- Brenner H, Werner S. Selecting a cut-off for colorectal cancer screening with a fecal immunochemical test. *Clin Transl Gastroenterol*. 2017;8(8):e111. doi:10.1038/ctg.2017.37.
- Liles EG, Perrin N, Rosales AG, et al. Performance of a quantitative fecal immunochemical test for detecting advanced colorectal neoplasia: a prospective cohort study. *BMC Cancer*. 2018;18(1):509. doi:10.1186/s12885-018-4402-x.
- Njor SH, Andersen B, Friis-Hansen L, et al. The optimal cut-off value in fit-based colorectal cancer screening: an observational study. *Cancer Med*. 2021;10(5):1872–1879. doi:10.1002/cam4.3761.
- van Turenhout ST, Oort FA, van der Hulst RWM, et al. Prospective cross-sectional study on faecal immunochemical tests: sex specific cut-off values to obtain equal sensitivity for colorectal cancer? *BMC Gastroenterol*. 2014;14(1):217. doi:10.1186/s12876-014-0217-7.
- Brenner H, Qian J, Werner S. Variation of diagnostic performance of fecal immunochemical testing for hemoglobin by sex and age: results from a large screening cohort. *Clin Epidemiol*. 2018;10:381–389. doi:10.2147/clep.S155548.
- Gies A, Niedermaier T, Alwers E, et al. Consistent major differences in sex- and age-specific diagnostic performance among nine faecal immunochemical tests used for colorectal cancer screening. *Cancers (Basel)*. 2021;13(14). doi:10.3390/cancers13143574.
- Levy BT, Xu Y, Daly JM, et al. Comparative performance of common fecal immunochemical tests. *Ann Intern Med*. 2024;177(10):1350–1360. doi:10.7326/M24-0080.