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Review article

# Performance of the fecal immunochemical test for colorectal cancer and advanced neoplasia in individuals under age 50

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ABSTRACT

The increased demand for colonoscopy combined with increased incidence of colorectal cancer (CRC) among younger populations presents a need to determine FIT performance among individuals in this age group. We conducted a systematic review to assess test performance characteristics of FIT in detecting CRC and advanced neoplasia in younger age populations. A search through December 2022 identified published articles assessing the sensitivity and specificity of FIT for advanced neoplasia or CRC among populations under age 50. Following the search, 3 studies were included in the systematic review. Sensitivity to detect advanced neoplasia ranged from 0.19 to 0.36 and specificity between 0.94 and 0.97 and the overall sensitivity and specificity were 0.23 (0.17–0.30) and 0.96 (0.94–0.98), respectively. Two studies that assessed these metrics in multiple age categories found similar sensitivity and specificity across all age groups 30–49. Sensitivity and specificity to detect CRC was assessed in one study and found no significant differences by age groups. These results suggest that FIT performance may be lower for younger individuals compared to those typically screened for CRC. However, there were few studies available for analysis. Given increasing recommendations to expand screening in younger age groups, more research is needed to determine whether FIT is an adequate screening tool in this population.

## 1. Introduction

Colorectal cancer (CRC) is among the leading causes of cancer-related morbidity and mortality worldwide among both women and men (Siegel et al., 2020; Brenner et al., 2019). Like many cancers, survival depends greatly on the stage of disease at cancer diagnosis; those diagnosed with localized disease have a 90% 5-year survival rate, whereas those diagnosed with metastatic disease have a 5-year survival of only 14% (Program, 2021). Screening with colonoscopy or fecal-based tests can help to determine the presence of precancerous polyps that have the potential to become cancerous (Ladabaum et al., 2020).

While colonoscopy is the gold-standard for CRC screening (Bénard et al., 2018), fecal immunochemical testing (FIT) is the most widely used tool as an index test in countries with population-based screening programs (Navarro et al., 2017). FIT has grown in popularity because it has higher diagnostic accuracy and higher adherence than guaiac-based fecal occult blood testing or colonoscopy, and is much less invasive than colonoscopy (Hewitson et al., 2008). The use of FIT for programmatic screening has contributed to decreases in incidence and mortality of CRC in screening-eligible populations (Siegel et al., 2020; Brenner et al., 2019). Screening recommendations have generally been developed using evidence among adults aged 50–74 (Lee et al., 2014), where

*Abbreviations:* CRC, colorectal cancer; FIT, fecal immunochemical test.

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its ability to detect pre-cancerous polyps and cost-effectiveness have been established. However, it is important to understand CRC prevention in younger age groups as newer research has shown a concerning trend of increasing incidence and mortality among younger adults who are not yet eligible for screening (Brenner et al., 2019; Siegel et al., 2019). In some cases, the incidence is equal to that observed in older populations prior to widespread screening (Lin et al., 2021). These trends prompted the United States Preventive Services Task Force (USPSTF) to change the lower limit of screening to age 45 (Davidson et al., 2021). However, as screening recommendations are largely based on performance of FIT among individuals in the screening eligibility age group (age 50–74), it is unclear whether the test would perform as well in younger individuals.

Given the increase in CRC in younger age groups and changing screening recommendations as observed from the USPSTF, it is important to understand the feasibility of screening these younger populations with FIT. These data are essential in non-US populations including single payer health care systems where cost effectiveness of changes to screening guidelines must be evaluated. Therefore, we conducted a systematic review to synthesize the availability evidence on the performance characteristics (sensitivity and specificity) of FIT in detecting CRC or precancers in individuals under the age of 50.

## 2. Methods

### 2.1. Overview and objectives

Our study was registered with PROSPERO during the initial inception for this systematic review (CRD42020193786). We utilized a standard systematic literature review processes using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; Moher et al., 2009). The PRISMA checklist for systematic reviews can be found in the Supplementary Materials. Our primary objective was to assess the test performance characteristics of FIT in populations under the age of 50.

### 2.2. Data sources and search strategy

We conducted searches of Ovid Medline and PubMed databases, with the detailed electronic search strategy provided in the Supplementary Materials. The electronic search was carried out from inception of the databases through March 15, 2020, and was updated through December of 2022. In addition to the electronic search, reference lists of other systemic reviews on FIT were reviewed manually and articles that met our search criteria were included.

### 2.3. Study selection

All relevant abstracts were imported into DistillerSR (Evidence Partners, Ottawa, Canada). Three authors (BM, TN, CR) independently screened all titles and abstracts that met the search criteria and in English-language were further reviewed for full text screening. Due to the broad search criteria and the number of abstracts included for full text, six authors (KC, CFS, BM, TN, JP, CR) independently reviewed full texts of potentially eligible studies. Any disagreements in this process were resolved by two authors (JP and EH).

### 2.4. Eligibility criteria

A study was included in data extraction if it met *all of* the following criteria:

1. It was a study written in English
2. It included participants under 50 years of age
3. It assessed performance characteristics (sensitivity, or specificity) of the FIT, or provided prevalence of positive and negative results and
4. The outcome measure was CRC, advanced adenoma, or advanced neoplasia. Advanced neoplasia refers to polyps larger than 10 mm in diameter, lesions with a villous component, severely dysplastic lesions, or invasive cancers. Colorectal cancers included colon cancer, rectal cancer, colorectal cancer, and adenocarcinomas of the colon or rectum. Advanced adenomas included adenomas with villous features or high-grade dysplasia, and larger 10 mm in size.

A study was excluded at any stage if it met *any* of the following criteria:

1. It was a commentary, review, editorial, or conference abstract,
2. It was published prior to 1990.

Studies were excluded if they were published before 1990 because FIT only started to be used for screening in the late 1980 s (Day et al., 2013), so anything published prior to 1990 would not be relevant for contemporaneous comparisons.

### 2.5. Statistical analysis

The pooled analysis of diagnostic accuracy was considered for studies with which the number of true-positives, false-positives, true-negatives, and false-negatives could be extracted for the outcome of colorectal cancer, advanced adenoma, or advanced neoplasia.

### 2.6. Data extraction, risk of bias assessments, and evidence summaries

Two authors (CFS and CR) independently extracted relevant data using a standardized extraction form. Each paper was extracted in duplicate by two authors to identify discrepancies and correct errors (EH, CFS). Data collected included study settings, population characteristics, total number of included participants, brand of FIT test used, FIT cut-off values for positivity, risk factors, sensitivity, specificity, positive and negative predictive value. When more than one cut-off value or threshold was used in a study, data was only extracted for 100 ng Hb/ml or an equivalent of 20 ug Hb/ug.

Risk of bias was assessed using the QUADAS-2 tool for systematic reviews on diagnostic tools (Whiting et al., 2011). These assessments were conducted by two authors (BM and PG) and were reviewed two others (TN and CR); any discrepancies were resolved through discussion.

## 3. Results

Our search strategy generated 1,861 citations for abstract review after duplicate removal, of which 1,214 were eligible for full text review. The high proportion of papers included for full-text review was attributed to the broad nature of the review, with multiple potentially eligible patient groups of interest and study designs. After screening, 1,203 were manually excluded and 3 studies were included (Kim et al., 2017; Jung et al., 2017; Chang et al., 2014). The greatest proportion of exclusions at the full text stage were removed because they did not assess the outcomes of interest for data inclusion in the analyses. The PRISMA diagram showing all stages of screening and exclusions can be found in Fig. 1. A description of the included studies can be found in Table 1.

All three studies were cross-sectional in design and originated in either Taiwan (Chang et al., 2014) or South Korea (Kim et al., 2017; Jung et al., 2017). The studies all assessed advanced neoplasia and only one assessed CRC as an outcome. The thresholds for positivity were not consistent at 10 ug Hb/g, 100 ng Hb/ml, and 20 ug/g. While we extracted data for multiple outcomes, only advanced neoplasia and CRC were analyzed because it they were the only outcomes reported.

Three studies examined FIT performance characteristics among individuals younger than the age of screening eligibility (<50 years). Overall FIT sensitivity for advanced neoplasia for individuals under 50 was 0.23 (95% CI 0.17–0.30); specificity for this outcome was 0.96 (95%

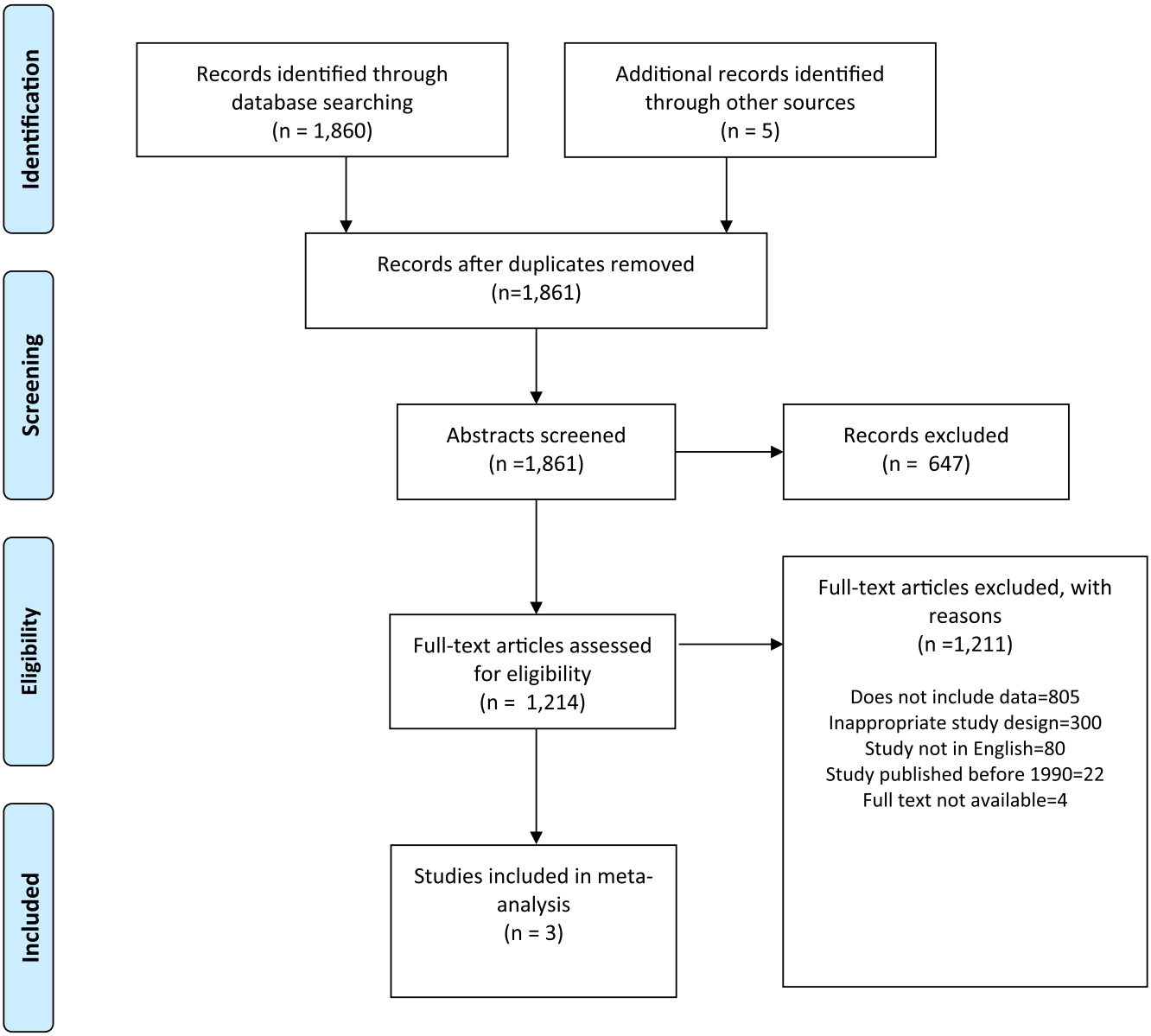


**Fig. 1.** PRISMA flowchart for selection of included studies.

**Table 1**
Description of included studies separated by population of interest.

| Author, year | Study design | Country | Cohort size (full cohort) | FIT brand | Threshold | Population of interest | Outcome(s) assessed | Prevalence of outcome (s) |
|---|---|---|---|---|---|---|---|---|
| Chang, 2014 | Cross-sectional | Taiwan | 10,884 | OC-LIGHT | 10 ug Hb/g | Age < 50 | Advanced neoplasia | Men: 2.1 %<br>Women: 1.2% |
| Jung, 2017 | Cross-sectional | South Korea | 19,808 | OC-SENSOR | 100 ng Hb/ml | Age < 50 | Advanced neoplasia | Age 30–34: 0.5 %<br>Age 35–39: 0.9 %<br>Age 40–44: 1.5 %<br>Age 45–49: 2.5% |
| Kim, 2017 | Cross-sectional | South Korea | 26,316 | OC-SENSOR | 20 ug/g | Age < 50 | CRC<br><br>Advanced neoplasia | Age 30–39: 0.008 %<br>Age 40–49: 0.03%<br>Age 30–39: 0.7 %<br>Age 40–49: 1.8% |

CI 0.94–0.98; Fig. 2). While all three studies assessed test performance for individuals under the age of 50, two studies provided results by age category (Kim et al., 2017; Jung et al., 2017). Two of the studies found that sensitivity and specificity to detect advanced neoplasia did not vary considerably by age group between 30 and 50 years of age, and neither study found differences between the younger age groups and ages over 50 years. The sensitivities for all ages under 50 in these studies were 0.19 (0.15–0.24; Jung et al., 2017) and 0.20 (0.16–0.24) and both reported specificities of 0.97 (0.97–0.98; Kim et al., 2017). The last study found a sensitivity considerably higher than the others at 0.36 (0.24–0.49) but

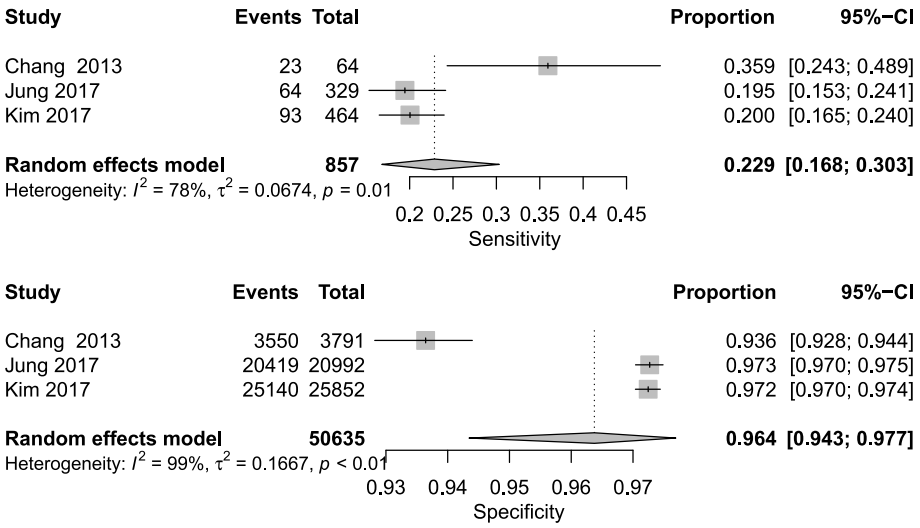


**Fig. 2.** Forest plot of included studies assessing FIT sensitivity (top) and specificity (bottom) to detect advanced neoplasia among younger adults.

found a comparable specificity of 0.94 (0.93–0.94; Chang et al., 2014), respectively. Only one study assessed sensitivity and specificity to detect CRC (Kim et al., 2017). Sensitivity and specificity among individuals aged 30–39 were 1.00 (0.025–1.00) and 0.97 (0.97–0.98), respectively. For those aged 40–49, sensitivity and specificity were 0.75 (0.19–0.99) and 0.97 (0.97–0.97), respectively. There were very few events in these age groups, but sensitivity and specificity were not significantly different compared to those for individuals above 50 years of age.

Study quality was assessed using the QUADAS-2 tool (Table 2). The studies had a moderate risk of bias and the categories with the highest risk of bias were patient selection and reference standard. The main concerns were that studies did not adequately describe how many patients were excluded during the study or why they were excluded, or it was not clear whether the reference standard was conducted without knowledge of the index test results.

## 4. Discussion

In this systematic review, we assessed the sensitivity and specificity of the FIT for detecting advanced neoplasia and CRC in individuals under the age of 50. Sensitivity and specificity for detecting advanced adenoma among individuals under 50 years of age were 0.23 and 0.96, respectively, from three studies. One study reported sensitivity and specificity to detect CRC and did not find a significant difference between the test performance among younger populations compared to older populations, though confidence intervals for sensitivity were very wide.

CRC is a common and deadly form of cancer and recent troubling trends point to a need to understand this disease better. As described in the introduction, while incidence and mortality for CRC in individuals over age 50 have decreased in the past decades, incidence for those younger than 50 years of age has increased in many populations worldwide (Brenner et al., 2019; Siegel et al., 2019; O'Sullivan et al., 2020). The causes of this increase are not well-understood so it is important to have secondary prevention methods in place to stop cancers from developing. In response to these trends, there have been some calls to reduce the age of screening eligibility from 50 to 45 years of age (Davidson et al., 2021); however, whether there will be widespread benefits from this change in policy remains unclear (Ladabaum et al., 2019; Mehta et al., 2021). Based on the changing screening guidelines and evidence of rising CRC rates in younger adults, it is important to conduct additional studies on FIT performance in adults under the age of 50. In order for other non-US jurisdictions to alter screening recommendations, detailed evaluations of efficacy, utility and cost-effectiveness are required. The findings of this study may guide these important evaluations.

Over the past two years, many non-emergency healthcare services were delayed or paused due to the strain caused by COVID-19 (Richards et al., 2020; Riera et al., 2021). Cancer screening services were halted in many settings, which has resulted in increased demand of colonoscopy following the easing of COVID-19-related disruptions (Kortlever et al., 2021; Chiu et al., 2021; Walker et al., 2022). To reduce the burden caused by this increased demand, it would be beneficial to establish recommendations for individuals at higher risk of CRC or for those outside current age eligibility who may otherwise receive colonoscopy. Employing the use of FIT for individuals younger than age 50 and giving only using colonoscopy as a second-line screening tool following confirmation of a positive FIT significantly improves the expected benefits of screening by dramatically reducing the number needed to screen (Chen et al., 2016). This means that colonoscopy use will be more efficient and fewer people will undergo unnecessary colonoscopies. The few studies presented in this synthesis also show that FIT may perform well in younger age populations and may be useful as a screening tool outside those presently screened. The accumulation of future evidence will help to establish a clearer idea of both the efficacy and cost-effectiveness of using FIT in these high-interest groups.

**Table 2**
Summarized risk of bias results of included studies based on the QUADAS-2 risk of bias tool.

| | Risk of bias | | | | Applicability concerns | | |
|---|---|---|---|---|---|---|---|
| Study | Patient selection | Index test | Reference standard | Flow and timing | Patient selection | Index test | Reference standard |
| Chang | | | | | | | |
| Jung | | | | | | | |
| Kim | | | | | | | |

Compared to FIT performance characteristics for individuals eligible for screening, our results demonstrate lower sensitivity and specificity in younger populations. A recent *meta*-analysis of FIT performance in average-risk adults over the age of 50 found sensitivity and specificity for advanced neoplasia as 0.68 (95% CI 0.64–0.72) and 0.81 (95% CI 0.77–0.84), respectively (Saw et al., 20222022). These results are for a FIT positivity threshold of 10 ug/g, which was the most common threshold reported among studies in our analysis. In another *meta*-analysis, sensitivity for detecting CRC was 0.91 (95% CI 0.84–0.95) and specificity was 0.91 (95% CI 0.50–0.83), also for a positivity threshold of 10 ug/g (Imperiale et al., 2019). These test performance characteristics should be expected, though, given the lower prevalence of lesions of interest in these younger populations. While sensitivity and specificity are not directly impacted by disease prevalence, lesions may be earlier in growth in this population compared to older populations, which may impact the ability of the test to detect positivity. Our results only come from three studies, though, so this comparison should be taken with caution.

The limitations of our study are similar to those reported by other *meta*-analyses assessing performance characteristics of FIT. First, we had an extremely limited number of studies to compare in the synthesis, and the studies were not similar in population size, brand of FIT, or FIT positivity threshold. Two studies presented test performance results with a cutoff value of 100 ng Hb/ml or an equivalent of 20 ug Hb/ug. However, one study used a threshold of 10 ug Hb/ug (Chang et al., 2014), which would potentially lead to changes in sensitivity and specificity. Second, we were also not able to compare sensitivity and specificity for CRC because only one study presented these results and had few events to analyze. Third, only studies written in English were included in this analysis, which may have excluded some relevant studies. Future studies should compare sensitivity and specificity by different positivity thresholds and FIT brands, and may need much larger populations and more diverse to assess performance in detecting cancers.

## 5. Conclusion

Our results suggest that the sensitivity and specificity for detecting advanced neoplasia in populations under 50 years of age are lower compared to sensitivity and specificity among populations typically screened. Despite lower performance, they still show promise in these lower age populations. However, these results should be interpreted with extreme caution due to the limitations of the included evidence base. Given the changing recommendations for some clinical populations of interest, further research is needed on FIT performance characteristics in these individuals. Specifically, studies should focus on identifying the optimal threshold for positivity and potentially including a narrower age range that may benefit most from early screening.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2023.102124.

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