Thieme

Sessile serrated polyp detection rates after fecal immunochemical test or multitarget stool DNA test: Systematic review and meta-analysis

OPEN ACCESS

Authors
Rajat Garg[1], Carol A. Burke[2], Manik Aggarwal[1], Carole Macaron[1], Amandeep Singh[2], Michelle K. Kim[2], Miguel Regueiro[2], Bhatt Amit[1], Prabhleen Chahal[2], Shashank Garg[3]

Institutions
1 Gastroenterology and Hepatology, Cleveland Clinic Foundation, Cleveland, United States
2 Internal Medicine, Cleveland Clinic Foundation, Cleveland, United States
3 Medicine, University of Arkansas System, Little Rock, United States

Keywords
Colorectal cancer, Polyps / adenomas / ..., Endoscopy Lower GI Tract, CRC screening

received 10.8.2023
accepted after revision 23.1.2024
accepted manuscript online 29.1.2024

Bibliography
Endosc Int Open 2024; 12: E474–E487
DOI 10.1055/a-2256-3411
ISSN 2364-3722

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Corresponding author
Dr. Rajat Garg, MD, Cleveland Clinic Foundation, Gastroenterology and Hepatology, Cleveland, United States
drgargrajat@gmail.com

Supplementary Material is available at https://doi.org/10.1055/a-2256-3411

ABSTRACT

Background and study aims Published studies report a higher adenoma detection rate (ADR) for FIT-DNA as compared with FIT. Data are less replete about the performance of stool-based tests for sessile serrated polyp (SSP) detection. We performed a meta-analysis to evaluate the performance of FIT and FIT-DNA testing for SSP detection rate (SSPDR) in patients undergoing colonoscopy for follow up of positive noninvasive tests.

Methods A comprehensive literature search of multiple databases (until September 2022) was performed to identify studies reporting SSPDR in patients with positive FIT or FIT-DNA tests. The outcome was overall colonoscopy detection of any SSPs and advanced serrated polyps (ASP: SSP ≥ 10 mm and/or dysplasia).

Results Included were 482,405 patients (52.4% females) with a mean age of 62.3 ± 4.4 years from 23 studies. The pooled SSPDR for all positive stool-based tests was 5.3% and higher for FIT-DNA (15.0%, 95% confidence interval [CI] 8.3–25.7) versus FIT (4.1%, 95% CI 3.0–5.6; P= 0.0002). The overall pooled ASP detection rate was 1.4% (95% CI 0.81–2.3) and higher for FIT-DNA (3.8 %, 95% CI 1.7–8.6) compared with FIT (0.71%, 95% CI 0.36–1.4; P<0.01). SSPDR with FIT-DNA was also significantly higher than FIT when the FIT cutoff was >10 ug/g and in FIT-positive patients in studies conducted in North America (P<0.05).

Conclusions FIT-DNA outperformed FIT in both SSP and ASP detection including FIT with a lower threshold cutoff of >10 ug/g. Further comparative studies are needed to assess the impact of our findings on colorectal cancer reduction.

‡ These authors share first authorship.

Introduction

Fecal immunochemical testing (FIT) and FIT-DNA testing are stool-based tests recommended for average risk colorectal cancer (CRC) screening by numerous organizations in the United States [1, 2, 3]. FIT detects human globin using monoclonal or polyclonal antibodies whereas FIT-DNA includes assay for mutant *KRAS*, methylated BMP3, and NDRG4, in combination with a FIT [4]. FIT is adopted as the primary CRC screening tool for the majority of European countries, Canada, and Australia and in programmatic approaches to screening in the United States [5]. The goal of stool testing is to identify early-stage CRC, but optimally, it would also detect benign precursors to CRC including advanced adenomatous or serrated polyps. Most CRCs develop from an adenoma while approximately 20% to 30% originate from sessile serrated polyps (SSPs) [1]. SSPs are presumed to result from mutations in genes responsible for cell proliferation and differentiation, such as the hypermethylation pathway, and tend to bleed less so they may not be detected with FIT testing [6]. Previous studies have also reported a higher adenoma detection rate (ADR) with FIT-DNA than with FIT and advanced SSPs; however, data on the SSP detection rate (SSPDR) with stool-based tests are less robust.

Therefore, we performed a meta-analysis aimed evaluating the SSPDR of FIT and FIT-DNA testing in patients undergoing colonoscopy for positive stool test follow up.

Methods

Search strategy

A comprehensive search of several databases was conducted from their inception to August 30, 2022. The databases included Ovid MEDLINE and Epub Ahead of Print, In-Process and other non-indexed citations, Ovid Embase, Ovid Cochrane Central Register of Controlled trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. An experienced medical librarian using inputs from the study authors helped with the literature search. Controlled vocabulary supplemented with keywords was used to search for studies of interest. The full search strategy is available in **Appendix 1**. The PRISMA and MOOSE checklist were followed and are provided in **Appendix 2** and **Appendix 3**[7, 8].

Study selection

We included studies that reported SSPDR from colonoscopy after a positive FIT or FIT-DNA in average-risk asymptomatic populations. Studies were included irrespective of the study sample size, setting, FIT cutoff, FIT test brand, number of FIT tested, or geography as long as data needed for the analysis were provided.

Studies done in a pediatric population (aged < 18 years), abstracts, studies not published in the English language, and not reporting primary outcome (SSPDR) were excluded. In case of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained.

Data abstraction and quality assessment

Data about study-related outcomes in the patient studies were abstracted onto a standardized form by at least two authors (RG, MA), and two authors (RG, MA) did the quality scoring independently. Any disagreements between authors about inclusion/exclusion criteria and quality scoring were discussed with the third author (SG) and final decisions were reached by mutual agreement. Primary study authors were contacted via email as needed for further information and/or clarification about data.

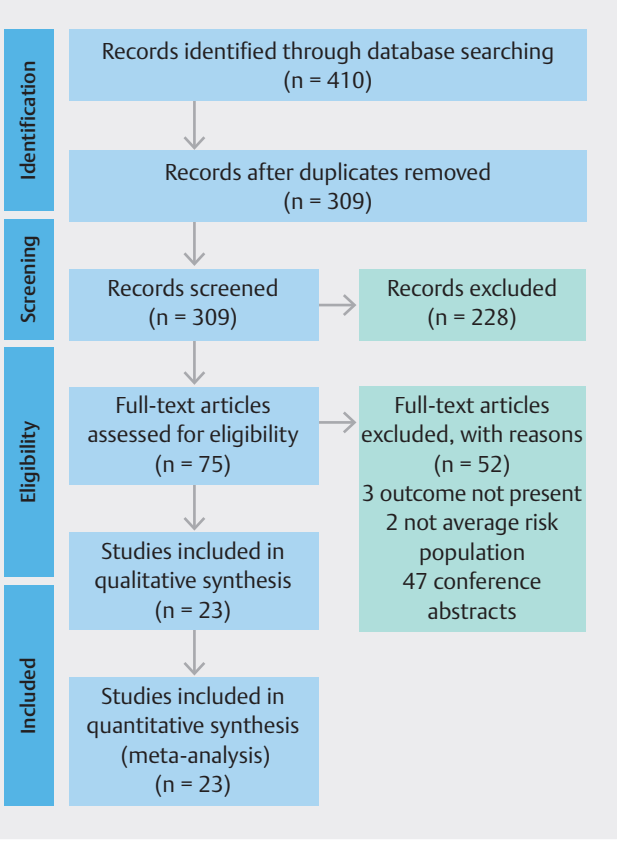
The Newcastle-Ottawa scale was used to assess the quality of cohort studies [9]. This quality score consisted of eight questions, the details of which are provided in **Supplementary Table 1**. The Jadad score was used for randomized trials [10].

Outcomes assessed

The primary outcome of the meta-analysis was pooled SSPDR. We further categorized serrated findings into advanced serrated polyp (ASP) detection rate (ASPDR) and proximal serrated polyp (PSP) detection rate. ASPs was defined as any serrated polyp ≥ 10 mm or with dysplasia and PSP was defined as any serrated polyp located proximal to the splenic flexure. SSPDR and ASPDR were compared between FIT and FIT-DNA cohorts. Subgroup analyses were performed based on FIT cutoff, continent, and study type.

Statistical analysis

Pooled estimates were calculated in each case following the methods suggested by DerSimonian and Laird using the random-effects model [11]. When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis [12]. Heterogeneity was assessed between study-specific estimates by using Cochran Q statistical test for heterogeneity and the I^2 statistics [13, 14]. In this, values of < 30%, 30% to 60%, 61% to 75%, and > 75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively [15]. Publication bias was ascertained, qualitatively, by visual inspection of funnel plot and quantitatively, with the Egger's test [16]. When publication bias was present, further statistics using the fail-Safe N test and Duval and Tweedie's "Trim and Fill" test was used to ascertain the impact of the bias [17, 18]. A Wald-type test was conducted to compare the summary effect sizes across subgroups: using either a Z-score or a Q-statistic (both yield the same *P* value), whether or not two groups had significantly different outcomes. $P \geq 0.05$ was used a-priori to define significance of the difference between compared groups. Meta-regression analyses were conducted using mixed level models and taking one predictor's influence at a time on the outcome. All analyses were performed using R statistical software (Metafor package).



▶ **Fig. 1** Study selection flow chart.

Results

Search results and population characteristics

A total of 410 studies were found on the initial search, of which 309 records were screened after removing duplicates. Seventy-five full-length articles were assessed for inclusion and 23 studies were included in the final analysis [19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41]. Sixteen studies reported SSPDR after only FIT testing [19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34], three reported SSPDR on both FIT and FIT-DNA [35, 36, 37], and three studies reported SSPDR after only FIT-DNA testing (▶ **Fig. 1**) [38, 39, 40, 41].

A total of 482,405 patients were included from 23 studies (▶ **Table 1**). The mean patient age was 62.3 ± 4.4 years including 52.4% females. A total of 355,319 patients were FIT positive in 19 studies and 5,087 were FIT-DNA positive from seven studies. Among the 355,319 FIT-positive and 5087 FIT-DNA-positive patients, 99.4% (N = 353,319) and 89.4% (N = 4,552) underwent subsequent colonoscopy, respectively. The FIT cutoff ranged from ≥ 4 to ≥ 55 ug/g in the included studies. The most common cutoff for FIT was ≥ 10 ug/g (N = 8 studies) followed by ≥ 20 ug/g from five studies. The most common FIT kit was OC-Sensor (N = 7 studies) followed by OC FIT-CHEK (N = 3 studies) (▶ **Table 1**). Eight studies reported FIT results in 237,647 screened patients whereby 15,089 (6.3%) were FIT positive and 13,089 (86.7%) patients underwent colonoscopy. All studies of FIT-DNA testing included multitargeted stool DNA (MT-sDNA). Six studies reported FIT-DNA results in which 24,549 screened patients were screened, 4,847 subjects (19.7%) tested positive, and 4,312 (88.9%) underwent colonoscopy (▶ **Table 2**).

Characteristics and quality of included studies

Nine studies were prospective, 13 were retrospective, and one was a randomized controlled trial. Among the 22 cohort studies, all were high-quality based on the Newcastle-Ottawa scale and one randomized trial was good-quality based on the Jadad scale (**Supplementary Table 1**).

Meta-analysis outcomes

The pooled SSPDR for all positive stool-based tests was 5.3% (95% confidence interval [CI] 4.0–6.9; I^2 = 99.5%) from 17 studies. The pooled SSPDR for FIT-DNA was 15.0% (95% CI 8.3–25.7; I^2 = 94.5%, 3 studies) which was significantly higher compared with FIT (4.1%, 95% CI 3.0–5.6; I^2 = 99.6%, 14 studies; P = 0.0002; ▶ **Fig. 2a**). The pooled ASPDR was 1.4% (95% CI 0.81–2.3; I^2 = 96.7%) and higher with FIT-DNA at 3.8 % (95% CI 1.7–8.6; I^2 = 92.8%) as compared with FIT (0.71%, 95% CI 0.36–1.4; I^2 = 75.4%; P < 0.01; ▶ **Fig. 2b**). The pooled rate of PSPs could only be calculated with FIT which was 4.6% (95% CI 2.9–6.9; I^2 = 99.9%; 8 studies ▶ **Fig. 2c**).

Subgroup analyses

Subgroup analyses were performed for SSPDR and ASPDR based on FIT cutoff (≥ 10 vs. 20 ug/g or FIT10 and FIT20 groups), continent (North America vs. Europe after FIT), study type (retrospective vs prospective after FIT), FIT vs FIT-DNA in North America and FIT10 vs. FIT-DNA. SSPDR in FIT-DNA was significantly higher than both FIT10 (15.0%; 95% CI 8.3–25.7; I^2 = 94.5%, 3 studies vs. 6.0%; 95% CI 5.2–6.8; I^2 = 94.6%, 7 studies, P < 0.001) (▶ **Fig. 3a**) and FIT group in NA (15.0%; 95% CI 8.3–25.7; I^2 = 94.5%, 3 studies vs. 7.1%; 95% CI 6.4–7.9; I^2 = 71.3%, 5 studies, P < 0.001) (▶ **Fig. 3b**). Pooled SSPDR was also significantly higher in FIT10 compared with FIT20 group (4.4%; 95% CI 3.2–6.1, I^2 = 94.6%, 7 studies vs. 2.1%; 95% CI1.4–3.1, I^2 = 99.6, 5 studies, P < 0.006). There were no significant differences in SSPDR after FIT between NA and Europe; and based on study type. These results are summarized in ▶ **Table 3**.

ASP detection rate was found to be significantly higher in prospective studies (1% vs 0.4%, P = 0.01) as compared with retrospective studies (▶ **Table 3**). There was a trend toward higher rates of ASPDR in FIT-DNA (3.8%, 95% CI, 2.3%-6.8% vs. 1.03%, 95% CI 0.39–2.69, P = 0.053) compared with FIT10. There was no difference in ASPDR based on FIT cutoff (≥ 10 vs. 20 ug/g) (P = 0.1) (▶ **Table 3**). Subgroup analyses comparing NA vs. Europe and FIT vs. FIT-DNA in NA were not possible due to the limited number of studies.

Meta-regression

Meta-regression was performed for the primary outcome of SSPDR based on age, gender, FIT cutoff, and study type, none of which had any significant predictive influence on SSPDR (P > 0.05 for all) (▶ **Table 4**).

▶ **Table 1** Study and population characteristics of FIT-screened population.

Author, year	Country	Study type	Number	Age (range or mean with SD) years	Females (%)	FIT details	Cutoff (ug/g) 50 ng/mL = 10 ug/g	FIT frequency	FIT screened	FIT positive	Colonoscopy	SSP (N, %)	PSP (N, %)	ASP (N, %)	SSPs included
Anderson et al, 2022	USA	Retrospective	51572	61–67	50.90%				NR	194	194	23 (11.8%)			Clinically relevant serrated polyps [including all traditional serrated adenomas, all sessile serrated polyps (SSP), and HPs ≥10 mm
Bleijenberg et al, 2020	Netherlands	Prospective	62341	66–71	41%	Cut off 275 ng/mL	55	Biennial	NR	62341	62341		6608 (10.60%		PSDR, proximal to descending colon
Bosch et al, 2019	Netherlands	Prospective trial	1426	50–75	49%	OC-Sensor cutoff 50 ng/mL	10		1047	60	1047			2 (3.3%)	ASP was defined as a serrated or hyperplastic polyp $1 cm and/or a serrated polyp with low- or high-grade dysplasia
Bronzwaer et al, 2020	Netherlands	Prospective trial	2889	66	38.60%	FOB gold Sentinel Milan, Italy (≥ 275 ng/mL)	55		NR	2889	2889		396 (13.70%)		proximal serrated polyp, defined as a hyperplastic polyp, sessile serrated lesion (SSL), or traditional serrated adenoma (TSA)

▶ **Table 1** (Continuation)

Author, year	Country	Study type	Number	Age (range or mean with SD) years	Females (%)	FIT details	Cutoff (ug/g) 50 ng/mL = 10 ug/g	FIT frequency	FIT screened	FIT positive	Colonoscopy	SSP (N, %)	PSP (N, %)	ASP (N, %)	SSPs included
Carot et al, 2018	Spain	Randomized trial	15670	50–69	55.60%	OC-Sensor (≥ 15 ug/g)	15		10,611	767	668	164 (21.4%)	44 (5.7%)		any SSP, traditional serrated adenoma (TSA) or hyperplastic polyp (HP)
Chang et al, 2017	Taiwan	Prospective	6198	59	48.90%	OC-Sensor (≥ 10, 15 or 20 ug/g)	10		6198	644	6198	11 (1.7%)		9 (1.4%)	WHO classification
Chu et al, 2022	Canada	Retrospective	74605	62	44.20%	"NS-Plus Alfresa Pharma Corporation Japan (10 ug/g)"	10	biennial	NR	74605	74605	5227 (7.0%)	3808 (5.1%)		SSP and/or TSA and/or HP
Cock et al 2019	Australia	Prospective	1882	63.4 ± 10.2	48.80%	OC-Sensor Eiken Chemical Co Tokyo, Japan (≥10 ug/g)	10		1882	519	519	10 (1.9%)		4 (0.8%)	World Health Organization (WHO) classification with diagnostic histologic features present in at least three crypts (or two adjacent crypts), no HP
Manzano-Robleda et al, 2020	Mexico	Retrospective	737	59.1 ± 6.3	69.90%	OC FIT-CHEK Polymedco ≥ 20 ng/mL (4 ug/g feces)	4	biennial	737	112	87	1 (0.89%)		0	sessile serrated polyps or the traditional serrated adenomas

▶ **Table 1** (Continuation)

Author, year	Country	Study type	Number	Age (range or mean with SD) years	Females (%)	FIT details	Cutoff (ug/g) 50 ng/mL = 10 ug/g	FIT frequency	FIT screened	FIT positive	Colonoscopy	SSP (N, %)	PSP (N, %)	ASP (N, %)	SSPs included
Denis et al, 2022	France	Prospective	13067	62.4 ± 7	40.30%	OC-Sensor (≥ 30 ug/g)	30	Annual	NR	13,067	13067		993 (7.60%)		NR
Grobbee et al, 2020	Netherlands	Prospective	30007	59–60	50%	≥ 10 mg Hb/g	10	Biennial	10743	2054	1879	158 (7.7%)			serrated polyp (hyperplastic, sessile serrated adenoma, traditional serrated adenoma)
Imperiale et al, 2014	USA	Prospective	9989	64.2 ± 8.4	53.70%	OC FIT-CHEK PolymedCo ≥ 100 ng/mL	20		9989	1148	9989			5 (0.4%)	NR
Kligman et al, 2018	USA	Retrospective	808	63.4 ± 6.3	96%	OC FIT-CHEK PolymedCo ≥ 20 ug/g	20		NR	207	207	9 (4.3%)			NR
Lund et al, 2019	Denmark	Retrospective	8256	63.9	47%	OC-Sensor ≥ 20 ug/g)	20	biennial	NR	8256	8256	25 (0.3%)			NR
Mowat et al, 2019	Scotland	Retrospective	1147			HM-JACK-arc Kyowa Medex Co., Ltd Tokyo, Japan (≥ 10 ug/g)	10		NR	1447	1447	12 (0.82%)	12 (0.82%)	6 (0.4%)	SSA + TSA

▶ **Table 1** (Continuation)

Author, year	Country	Study type	Number	Age (range or mean with SD) years	Females (%)	FIT details	Cutoff (ug/g) 50 ng/mL = 10 ug/g	FIT frequency	FIT screened	FIT positive	Colonoscopy	SSP (N, %)	PSP (N, %)	ASP (N, %)	SSPs included
O'Reilly et al, 2021	Ireland	Retrospective	9785			100 to 225 ngHb/mL	20		196, 440	9785	8084	730 (7.5%)			histological criteria-architectural disturbance of crypt bases/"boot-shape" crypts; at least 3 abnormal crypts; serrations and mature mucinous cells at the crypt bases; lacking the complexity of tubular adenomas, with our without evidence of dysplasia.
Telford et al, 2021	Canada	Retrospective	1043-26	62	45%	NS-Plus Alfresa Pharma Japan (≥ 10 ug/g)	10	biennial	NR	10432-6	104326	7402 (7.1%)	5889 (5.6%)		NR

▶ **Table 1** (Continuation)

Author, year	Country	Study type	Number	Age (range or mean with SD) years	Females (%)	FIT details	Cutoff (ug/g) 50 ng/mL = 10 ug/g	FIT frequency	FIT screened	FIT positive	Colonoscopy	SSP (N, %)	PSP (N, %)	ASP (N, %)	SSPs included
Van Doorn et al, 2015	Netherlands	Retrospective	2133	60 ± 6.7	47%	OC-Sensor Eiken Chemical Co Tokyo, Japan (≥ 10 ug/g)	10	biennial	NR	877	877	85 (9.7%)			Hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas were grouped as serrated lesion
Zorzi et al, 2017	Italy	Retrospective	72021	61.3	43%	Cut-off 20 mg HB/fecal g	20	biennial	NR	72021	72021	1295 (1.8%)	585 (0.8%)	282 (0.39%)	hyperplastic and SSPs

FIT, fecal immunochemical test; SSP, sessile serrated polyps/lesions; PSP, proximal sessile serrated polyp/lesion; ASP, advanced serrated lesion.

▶ **Table 2** Study and population characteristics of FIT-DNA screened population.

Author, year	Country	Study type	Age (range or mean with SD) years	Female (%)	FIT-DNA screened	FIT-DNA positive	Colonoscopy	SSPDR (N, %)	ASP (N, %)	SSP Included
Anderson et al, 2022	USA	Retrospective	61–67	50.90%		240	240	51 (21.2%)		Clinically relevant serrated polyps [including all traditional serrated adenomas, all sessile serrated polyps (SSP), and HPs ≥ 10 mm
Bosch et al, 2019	Netherlands	Prospective trial	50–75	49%	1014	94	94		11 (11.7%)	ASP was defined as a serrated or hyperplastic polyp ≥ 1 cm and/or a serrated polyp with low- or high-grade dysplasia
Deiss-Yehiely et al, 2022	USA	Retrospective	63.8 ± 9	64%	3987	605	476		26 (4.3%)	only SSA ≥ 10 mm or dysplasia, no TSA or HP
Imperiale et al, 2022	USA	Prospective	47.8 ± 1.5	47.70%	816	53	53		1 (1.9%)	Serrated lesions ≥ 10 mm
Imperiale et al, 2014	USA	Prospective	64.2 ± 8.4	53.70%	9989	2652	2652		42 (1.6%)	NR
Johnson et al, 2017	USA	Retrospective	69	62%	1908	201	132	36 (17.9%)		NR
Vakil et al, 2020	USA	Retrospective	65 ± 8	57.90%	6835	1242	905	110 (8.8%)		NR

FIT, fecal immunochemical test; SD, standard deviation; SSP, sessile serrated polyp/lesion; DR, detection rate; PSSP, proximal sessile serrated polyp/lesion; ASP, advanced serrated lesion; TSA, traditional serrated adenoma; HP, hyperplastic polyp.

Validation of meta-analysis results

Sensitivity analysis

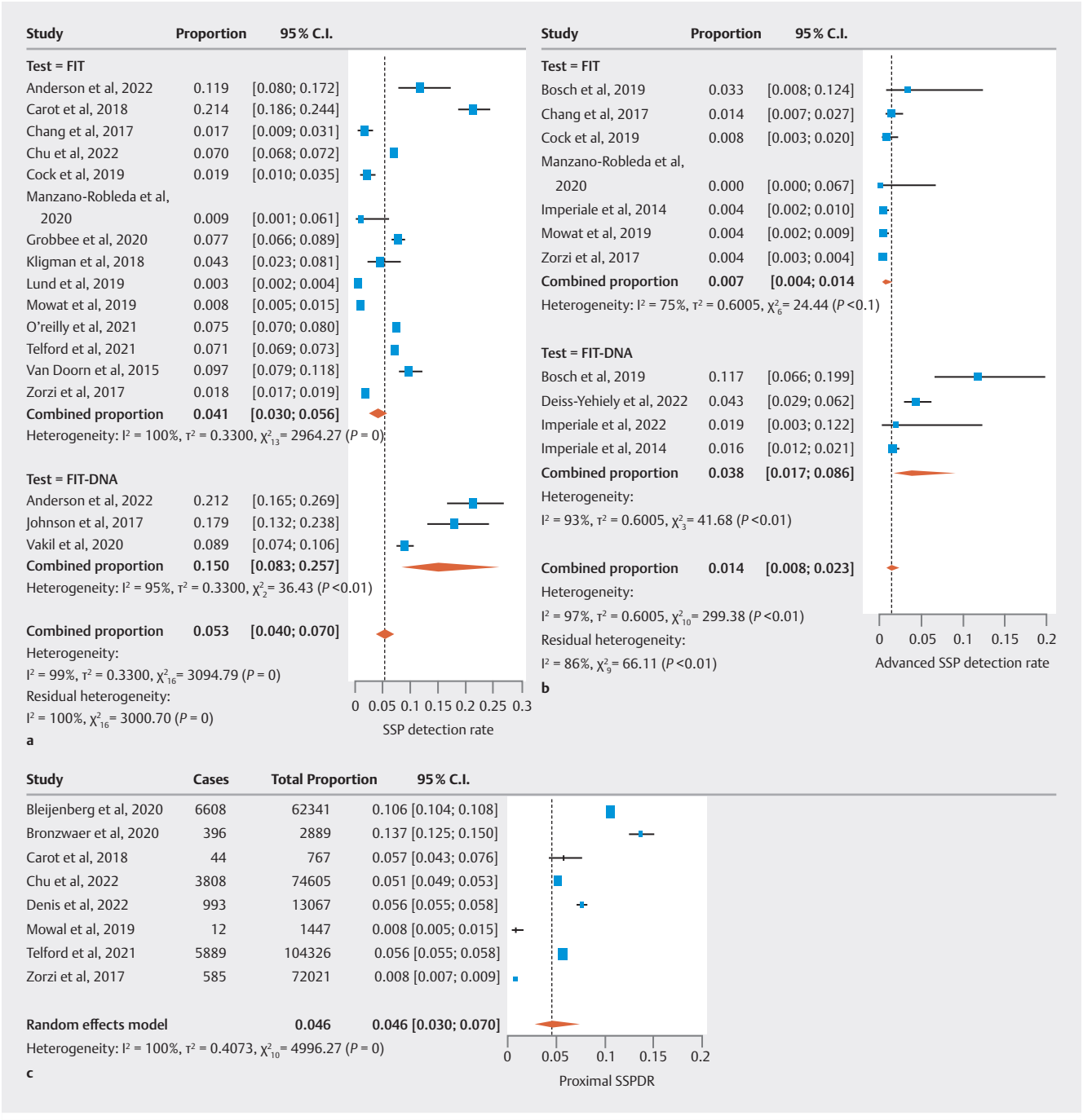
To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. On this analysis, Zorzi et al had significant influence on SSPDR for all stool-based screening tests [34]. After excluding that study, the pooled SSPDR for all stool-based tests changed to 6.3% (95% CI, 5.4–7.4%, I^2 = 97.7%).

Publication bias

Based on visual inspection of the funnel plot as well as quantitative measurement that used the Egger regression test, there was evidence of publication bias (**Supplementary Fig. 1**, Eggers 2-talied P = 0.001). On further trim and fill analysis, SSPDR was adjusted to 6.3% (95% CI, 4.7–8.2, 1 study added). Based on the overlapping confidence interval, the impact of publication bias was considered minimal.

Discussion

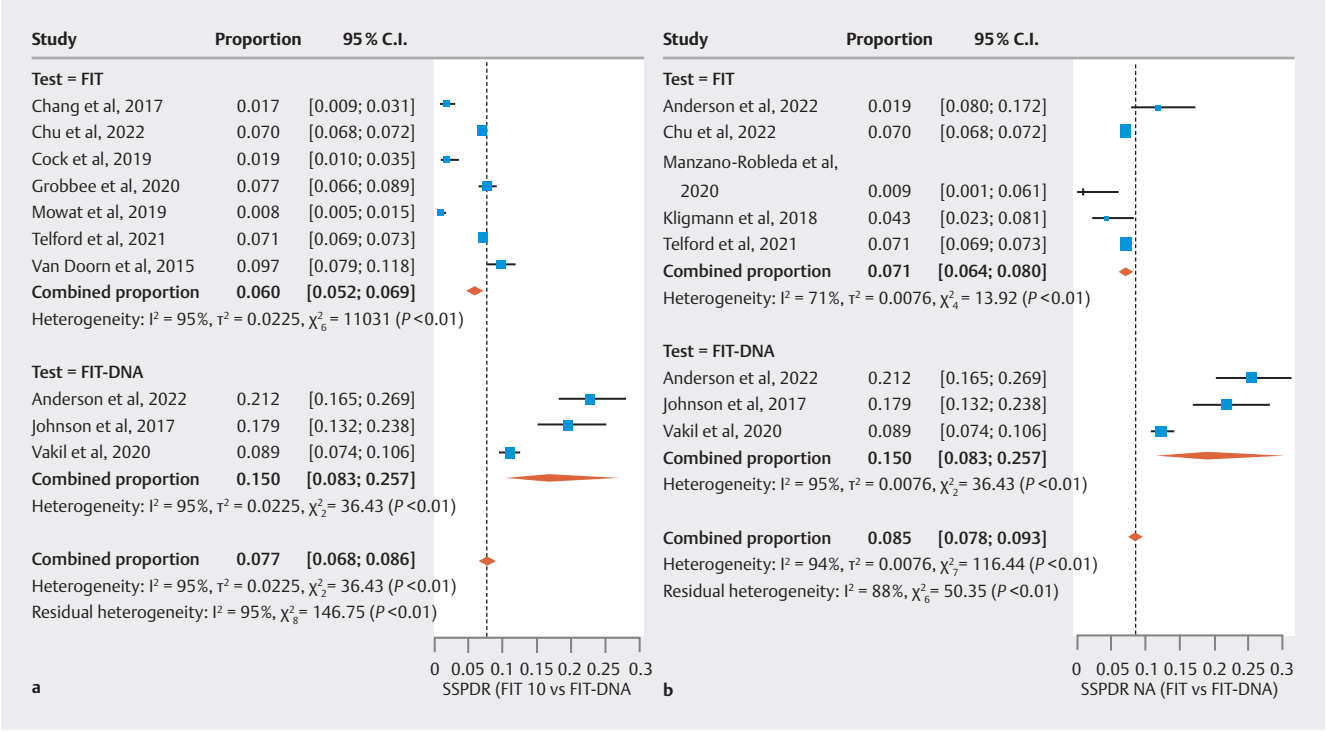
In this large meta-analysis of approximately 500,000 patients undergoing stool-based colorectal cancer screening, the pooled SSPDRs and ASPDRs for stool-based tests were 5.3% and 1.4%, respectively. The pooled SSPDR with FIT-DNA was significantly higher (15%) compared with FIT (4.1%). This remained true for ASPDR as well (3.8% vs. 0.71%, P < 0.01). This is the first meta-analysis reporting SSPDR on colonoscopy



▶ **Fig. 2** Forest plot showing **a** pooled SSP, **b** ASP, and **c** proximal SSP detection rate in average risk patients screened with stool-based tests.

done for follow up after a positive stool-based CRC screening test.

SSP detection and resection is important to reduce CRC and establishing a benchmark for SSPDR on colonoscopy after a positive stool-based test would be of importance. SSPs are more difficult to detect endoscopically than adenomas due to their flat morphology and indistinct borders [4] and detection can be improved with longer withdrawal times, training, and visual and technological aids [42, 43]. It has been recently suggested that the SSPDR goal should be ≥ 7% for screening colonoscopy [44]. Significantly lower post-colonoscopy CRC rates have been noted in providers with clinically significant SSPDRs of 3% to 9% vs. 3% even in endoscopists with high ADRs (>25%) [45]. Currently, comparative data on detection of serrated lesions in patients undergoing colonoscopy after positive stool-based testing are limited. Our study reports significantly higher SSP and ASP detection rates after positive FIT-DNA as compared with positive FIT testing. Prior observations demonstrate that FIT-DNA has a higher sensitivity for detecting conventional adenomas including advanced adenomas as compared with FIT [35,



▶ **Fig. 3** Forest plot showing pooled SSPDR in **a** FIT-DNA-positive vs. FIT10 group and **b** FIT-DNA vs. FIT in North American cohort.

36, 46]. These findings provide information with which to counsel patients about the utility of one versus the other test. Detection of methylated pathway aberrations in SSPs by FIT-DNA and lack of bleeding of SSPs are the most likely reason for higher detection versus FIT [47]. Literature suggests that this increased detection or sensitivity of FIT-DNA for premalignant polyps is associated with a reduced specificity that leads to false-positive results and increased health care costs [48]. Data about cost-effectiveness of FIT-DNA as compared with FIT are contradictory [49, 50, 51]. In one modeling study, annual FIT and colonoscopy every 10 years were found to be more cost-effective than FIT-DNA every 3 years with equal participation rates for all strategies, whereas another study reported FIT-DNA to be more cost-effective than FIT or colonoscopy and led to the highest quality-adjusted life-years savings [50, 51, 52]. Further studies can help determine the favorability of FIT-DNA over FIT test in terms of cost-effectiveness and screening interval.

Subgroup analysis also provided some interesting findings. A higher SSPDR was noted in the FIT10 group vs. the FIT20 group (4.4% vs. 2.1%). This is not surprising because decreasing FIT cutoff has been reported to have higher sensitivity for detecting conventional adenomas and CRC [53, 54, 55, 56]. However, FIT10 group still had a lower SSPDR as compared with FIT-DNA (5.9% vs. 15%), suggesting that FIT-DNA outperformed FIT for SSPs even at its lowest level of hemoglobin detection, further supporting the use of FIT-DNA for detecting these lesions. SSPDR was higher with FIT-DNA as compared with FIT in studies conducted in North America, which should support the use of FIT-DNA over FIT for CRC screening in this population. ASP was higher in prospective studies than in retrospective studies. The reasons for this finding are not entirely clear. A few potential explanations include increased awareness about SSPs among physicians performing screening colonoscopies that would impact SSPDR in prospective studies a lot more than in retrospective studies. It could also be a result of the Hawthorne effect among physicians participating in prospective studies, which is unlikely to be present in retrospective studies. There was no statistically significant difference in detection of ASPs in FIT-DNA vs. FIT10 or between the FIT10 and FIT 20 groups. This is most likely due to the small sample size, as only three studies provided data for these subgroups.

Our study has several important implications. First, SSPDR appears to be an important quality metric for colonoscopy. The lesions which should be included in the definition and additional studies on post-colonoscopy CRC are important because previous studies have used variable definition for SSPs, such as SSPDR, PSP detection rate, or clinically significant SSP detection [57]. In addition, SSPDR as a colonoscopy quality metric also depends on pathologic diagnosis due to the high degree of interobserver variation in pathologic determination of SSPs [58]. SSP definition along with pathologic examination will also need to be standardized before it can be accepted as a quality measure of colonoscopy [58]. The higher rate of detection of SSPs with FIT-DNA comes at cost of poor specificity, which can lead to heightened anxiety in both patients and colonoscopist. Based on current evidence, FIT-DNA clearly outperforms FIT for SSP detection even when compared with the lowest FIT cutoff. Whether this higher detection of SSPs translates into decreased incidence of CRC will need to be determined in future

▶ **Table 3** Summary of pooled rates on subgroup analysis.

Subgroup	SSP detection rate*	P value	ASP detection rate*	P value
FIT-10 vs FIT-DNA		**< 0.0001**		0.053
FIT ≥ 10 ug/g	5.8% (5.0–6.7), I2 = 94.6%, 7 studies		1.03% (0.39–2.69), I2 = 66.1%, 4 studies	
FIT-DNA	15.0% (8.3–25.7), I2 = 94.5%, 3 studies		3.81% (1.52–9.24), I2 = 92.8%, 4 studies	
FIT by cutoff		**0.004**		0.101
FIT ≥ 10 ug/g	4.4% (3.2–6.1), I^2 = 94.6%, 7 studies		0.98% (0.53–1.81), I^2 = 66.1%, 4 studies	
FIT ≥20 ug/g	2.1% (1.4- 3.1), I^2 = 99.6, 5 studies		0.48% (0.26–0.87), I^2 = 15.1%, 3 studies	
North America		**< 0.0001**		
FIT	7.2% (6.3–8.2), I^2 = 71.3%, 5 studies		only 2 studies	
FIT-DNA	15.0% (8.3–25.7), I^2 = 94.5%, 3 studies			
Continent		*P* = 0.09		
North America	6.5% (3.9–10.5), I^2 = 71.3, 5 studies		only 2 studies	
Europe	3.9% (2.6–5.6), I^2 = 99.7, 7 studies			
Study type		0.19		**0.018**
Retrospective	3.6% (2.5–5.2), I^2 = 99.7%, 10 studies		0.4% (0.23–0.68), I^2 = 0, 3 studies	
Prospective	5.6% (3.2–9.8), I^2 = 98.3, 4 studies		1% (0.58–1.7), I^2 = 61%, 4 studies	

Values are pooled rate, 95% Confidence interval, I^2 and number of studies.
SSP, sessile serrated polyp; ASP, advanced serrated polyp; FIT, fecal immunochemical test.
Bold indicates significant *P* values.

▶ **Table 4** Meta-regression results of SSP detection rate with various factors.

Factor	Coefficient with 95% CI	P value
Age	–0.19 (–0.41- 0.025)	0.08
Female gender	0.56 (–2.1–3.19)	0.67
Fit cutoff	–0.04 (–0.11–0.012)	0.11
Retrospective	–0.47 (–1.18–0.23)	0.19

studies. In addition, different screening intervals, qualitative vs quantitative FIT, and different test kits all add to variability in FIT performance. In the era of moving toward noninvasive screening modalities, FIT-DNA with a wider screening interval is likely going to outperform FIT, but its long-term impact on further decreasing CRC incidence and mortality remains to be seen.

This review has several strengths. We performed a systematic literature search with well-defined inclusion criteria. Redundant studies were careful excluded and only medium- to high-quality studies were included. The pooled sample size of included patients was large with narrow CIs for most estimates. This also allowed for various subgroup analyses and meta-regression. There are several limitations to this study. The included studies were mostly reported from tertiary care referral centers and may not be entirely representative of the general population. Retrospective studies included in the analysis could have contributed to selection bias. Various FIT studies had dissimilar designs in terms of interval to repeat FIT test, cutoff for hemoglobin in the stool sample, and use of one vs. multiple FITs for one-time screening. In addition, variable definitions of SSPs contributing to multiplicity issues and comparison of summary effects using the Z-score or q-statistics, which primarily report on the presence or absence of heterogeneity between groups, also added to limitations of our study. We did not account for synchronous adenomas because previous studies have reported on FIT performance for adenomas. There was presence of publication bias but its impact is considered minimal; however, we were unable to account for other reporting biases such as citation bias or outcome reporting bias, which influenced how likely it was that a finding will end up in our meta-analysis. All these factors could have contributed to the significant heterogeneity in the results. However, most of these limitations are inherent in any meta-analysis and an attempt was made to address these issues with various statistical methods, including subgroup analysis, sensitivity analysis, and meta-regression.

Conclusions

In conclusion, our meta-analysis demonstrates that FIT-DNA seems to detect a higher proportion of SSPs and ASPs as compared with FIT in a population at average risk for CRC. Further head-to-head studies are needed to ascertain the CRC mortality reduction with the use of FIT-DNA as compared with FIT.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Shaukat A, Kahi CJ, Burke CA et al. ACG Clinical Guidelines: Colorectal Cancer Screening 2021. Am J Gastroenterol 2021; 116: 458–479 doi:10.14309/ajg.0000000000001122

[2] Rex DK, Boland CR, Dominitz JA et al. Colorectal cancer screening: Recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc 2017; 86: 18–33

[3] Lin JS, Piper MA, Perdue LA et al. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2016; 315: 2576–2594 doi:10.1001/jama.2016.3332

[4] Imperiale TF, Ransohoff DF, Itzkowitz SH. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014; 371: 187–188 doi:10.1056/NEJMoa1311194

[5] Jensen CD, Corley DA, Quinn VP et al. Fecal immunochemical test program performance over 4 rounds of annual screening: a retrospective cohort study. Ann Intern Med 2016; 164: 456–463 doi:10.7326/M15-0983

[6] Rex DK, Ahnen DJ, Baron JA et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012; 107: 1315–1329

[7] Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. Ann Intern Med 2009; 151: 264–269 doi:10.1371/journal.pmed.1000097

[8] Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–2012 doi:10.1001/jama.283.15.2008

[9] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Europ J Epidemiol 2010; 25: 603–605 doi:10.1007/s10654-010-9491-z

[10] Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1–12 doi:10.1016/0197-2456(95)00134-4

[11] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–188 doi:10.1016/0197-2456(86)90046-2

[12] Sutton AJ, Abrams KR, Jones DR et al. Methods for meta-analysis in medical research. John Wiley & Sons Ltd; 2000

[13] Kanwal F, White D. "Systematic reviews and meta-analyses" in Clinical Gastroenterology and Hepatology. Clin Gastroenterol Hepatol 2012; 10: 1184–1186 doi:10.1016/j.cgh.2012.09.019

[14] Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557 doi:10.1136/bmj.327.7414.557

[15] Guyatt GH, Oxman AD, Kunz R et al. GRADE guidelines: 7. Rating the quality of evidence – inconsistency. J Clin Epidemiol 2011; 64: 1294–1302 doi:10.1016/j.jclinepi.2011.03.017

[16] Easterbrook PJ, Gopalan R, Berlin JA et al. Publication bias in clinical research. Lancet 1991; 337: 867–872 doi:10.1016/0140-6736(91)90201-y

[17] Duval S, Tweedie R. Trim and fill: A simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56: 455–463 doi:10.1111/j.0006-341x.2000.00455.x

[18] Rothstein HR, Sutton AJ, Borenstein M. Publication bias in meta-analysis: Prevention, assessment and adjustments. John Wiley & Sons; 2006

[19] Bleijenberg AGC, van Leerdam ME, Bargeman M et al. Substantial and sustained improvement of serrated polyp detection after a simple educational intervention: results from a prospective controlled trial. Gut 2020; 69: 2150–2158

[20] Bronzwaer MES, Vleugels JLA, Van Doorn SC et al. Are adenoma and serrated polyp detection rates correlated with endoscopists' sensitivity of optical diagnosis? Endoscopy 2020; 52: 763–772

[21] Carot L, Castells A, Hernandez C et al. Detection of serrated lesions in proximal colon by simulated sigmoidoscopy vs faecal immunochemical testing in a multicentre, pragmatic, randomised controlled trial. United European Gastroenterol J 2018; 6: 1527–1537 doi:10.1177/2050640618804722

[22] Chang LC, Shun CT, Hsu WF et al. Fecal immunochemical test detects sessile serrated adenomas and polyps with a low level of sensitivity. Clin Gastroenterol Hepatol 2017; 15: 872–879.e871

[23] Chu JE, Hamm J, Gentile L et al. Serrated lesion detection in a population-based colon screening program. J Clin Gastroenterol 2022; 56: 243–248 doi:10.1097/MCG.0000000000001519

[24] Cock C, Anwar S, Byrne SE et al. Low sensitivity of fecal immunochemical tests and blood-based markers of DNA hypermethylation for detection of sessile serrated adenomas/polyps. Digest Dis Sci 2019; 64: 2555–2562 doi:10.1007/s10620-019-05569-8

[25] Del Carmen Manzano-Robleda M, Espinosa-Tamez P, Potter MB et al. Fecal immunologic test results and diagnostic colonoscopy in a Mexican population at average risk for colorectal cancer. Cancer Prev Res 2020; 13: 959–965

[26] Denis B, Gendre I. Colonoscopy may be weak link in organised colorectal cancer screening programme with faecal immunochemical test. Journal of medical screening 2022; 29: 84–91 doi:10.1177/09691413211061118

[27] Grobbee EJ, Vlugt M van der, van Vuuren AJ et al. Diagnostic yield of one-time colonoscopy vs one-time flexible sigmoidoscopy vs multiple rounds of mailed fecal immunohistochemical tests in colorectal cancer screening. Clin Gastroenterol Hepatol 2020; 18: 667–675.e661

[28] Kligman E, Li W, Eckert GJ et al. Adenoma detection rate in asymptomatic patients with positive fecal immunochemical tests. Dig Dis Sci 2018; 63: 1167–1172

[29] Lund M, Erichsen R, Valori R et al. Data quality and colonoscopy performance indicators in the prevalent round of a FIT-based colorectal cancer screening program. Scandinavian J Gastroenterol 2019; 54: 471–477 doi:10.1080/00365521.2019.1597158

[30] Mowat C, Digby J, Strachan JA et al. Low sensitivity of fecal immunochemical tests (FIT) for detection of sessile serrated adenomas/polyps confirmed over clinical setting, geography, and FIT system. Dig Dis Sci 2019; 64: 3024–3026 doi:10.1007/s10620-019-05661-z

[31] O'Reilly SM, MacNally S, O'Donoghue D et al. Correlation of fecal immunochemical testing levels with pathology results in a national colorectal cancer screening program. Clin Transl Gastroenterol 2021; 12: e00277

[32] Telford J, Gondara L, Pi S et al. Higher adenoma detection, sessile serrated lesion detection and proximal sessile serrated lesion detection are associated with physician specialty and performance on di-

rect observation of procedural skills. BMJ Open Gastroenterol 2021; 8: e000677

[33] Van Doorn SC, Stegeman I, Stroobants AK et al. Fecal immunochemical testing results and characteristics of colonic lesions. Endoscopy 2015; 47: 1011–1017 doi:10.1055/s-0034-1392412

[34] Zorzi M, Senore C, Da Re F et al. Detection rate and predictive factors of sessile serrated polyps in an organised colorectal cancer screening programme with immunochemical faecal occult blood test: The EQuIPE study (Evaluating Quality Indicators of the Performance of Endoscopy). Gut 2017; 66: 1233–1240

[35] Anderson JC, Robinson CM, Hisey W et al. Colonoscopy findings in FIT + and mt-sDNA + patients versus in colonoscopy-only patients: New Hampshire Colonoscopy Registry data. Cancer Prev Res 2022; 15: 455–464 doi:10.1158/1940-6207.CAPR-21-0581

[36] Bosch LJW, Melotte V, Mongera S et al. Multitarget stool DNA test performance in an average-risk colorectal cancer screening population. Am J Gastroenterol 2019; 114: 1909–1918 doi:10.14309/ajg.0000000000000445

[37] Imperiale TF, Ransohoff DF, Itzkowitz SH et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014; 370: 1287–1297 doi:10.1056/NEJMoa1311194

[38] Deiss-Yehiely N, Graffy PM, Weigman B et al. Detection of high-risk sessile serrated lesions: multitarget stool DNA Versus CT colonography. Am J Roentgenol 2022; 218: 670–676 doi:10.2214/AJR.21.26719

[39] Imperiale TF, Kisiel JB, Itzkowitz SH et al. Specificity of the multi-target stool DNA test for colorectal cancer screening in average-risk 45–49 year-olds: a cross-sectional study. Cancer Prev Res 2021; 14: 489–496 doi:10.1158/1940-6207.CAPR-20-0294

[40] Johnson DH, Kisiel JB, Burger KN et al. Multitarget stool DNA test: clinical performance and impact on yield and quality of colonoscopy for colorectal cancer screening. Gastrointest Endosc 2017; 85: 657–665.e651

[41] Vakil N, Ciezki K, Huq N et al. Multitarget stool DNA testing for the prevention of colon cancer: outcomes in a large integrated healthcare system. Gastrointest Endosc 2020; 92: 334–341 doi:10.1016/j.gie.2019.12.027

[42] Butterly L, Robinson CM, Anderson JC et al. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire Colonoscopy Registry. Am J Gastroenterol 2014; 109: 417–426

[43] Shaukat A, Tuskey A, Rao VL et al. Interventions to improve adenoma detection rates for colonoscopy. Gastrointest Endosc 2022; 96: 171–183 doi:10.1016/j.gie.2022.03.026

[44] Keswani RN, Crockett SD, Calderwood AH. AGA Clinical Practice Update on Strategies to Improve Quality of Screening and Surveillance Colonoscopy: Expert Review. Gastroenterology 2021; 161: 701–711 doi:10.1053/j.gastro.2021.05.041

[45] Anderson JC, Hisey W, Mackenzie TA et al. Clinically significant serrated polyp detection rates and risk for postcolonoscopy colorectal cancer: data from the New Hampshire Colonoscopy Registry. Gastrointest Endosc 2022; 96: 310–317

[46] Imperiale TF, Ransohoff DF, Itzkowitz SH et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 2004; 351: 2704–2714 doi:10.1056/NEJMoa033403

[47] Anderson JC, Robertson DJ. Serrated Polyp detection by the fecal immunochemical test: an imperfect FIT. Clin Gastroenterol Hepatol 2017; 15: 880–882 doi:10.1016/j.cgh.2016.11.014

[48] Knudsen AB, Rutter CM, Peterse EFP et al. Colorectal Cancer Screening: An Updated Decision Analysis for the US Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2021 May. Report No.: 20–05271-ER2.

[49] Itzkowitz SH, Ahlquist DA. The Case for a multitarget stool DNA test: A closer look at the cost effectiveness model. Gastroenterology 2017; 152: 1620–1621 doi:10.1053/j.gastro.2016.11.058

[50] Ladabaum U, Mannalithara A. Comparative effectiveness and cost effectiveness of a multitarget stool DNA test to screen for colorectal neoplasia. Gastroenterology 2016; 151: 427–439 e426 doi:10.1053/j.gastro.2016.06.003

[51] Redwood DG, Dinh TA, Kisiel JB et al. Cost-effectiveness of multitarget stool DNA testing vs colonoscopy or fecal immunochemical testing for colorectal cancer screening in Alaska Native people. Mayo Clin Proc 2021; 96: 1203–1217 doi:10.1016/j.mayocp.2020.07.035

[52] Sharma T. Analysis of the effectiveness of two noninvasive fecal tests used to screen for colorectal cancer in average-risk adults. Public Health 2020; 182: 70–76 doi:10.1016/j.puhe.2020.01.021

[53] Lee JK, Liles EG, Bent S et al. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med 2014; 160: 171 doi:10.7326/M13-1484

[54] Imperiale TF. Quantitative immunochemical fecal occult blood tests: is it time to go back to the future? Ann Intern Med 2007; 146: 309–311 doi:10.7326/0003-4819-146-4-200702200-00013

[55] Wieten E, Schreuders EH, Nieuwenburg SA et al. Effects of increasing screening age and fecal hemoglobin cutoff concentrations in a colorectal cancer screening program. Clin Gastroenterol Hepatol 2016; 14: 1771–1777 doi:10.1016/j.cgh.2016.08.016

[56] Burke CA, Lieberman D, Feuerstein JD. AGA Clinical Practice Update on Approach to the Use of Noninvasive Colorectal Cancer Screening Options: Commentary. Gastroenterology 2022; 162: 952–956 doi:10.1053/j.gastro.2021.09.075

[57] Macaron C, Rouphael C, Burke CA. Setting a benchmark for serrated polyp detection rate: defining the target and terminology comes first. Gastrointest Endosc 2022; 96: 318–320 doi:10.1016/j.gie.2022.04.022

[58] Vennelaganti S, Cuatrecasas M, Vennalaganti P et al. Interobserver agreement among pathologists in the differentiation of sessile serrated from hyperplastic polyps. Gastroenterology 2021; 160: 452–454 e451