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SPECIAL ARTICLE

Recommendations on fecal immunochemical testing to screen for colorectal neoplasia: a consensus statement by the US Multi-Society Task Force on colorectal cancer

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The use of the fecal occult blood test (FOBT) for colorectal cancer (CRC) screening is supported by randomized trials demonstrating effectiveness in cancer prevention and widely recommended by guidelines for this purpose. The fecal immunochemical test (FIT), as a direct measure of human hemoglobin in stool has a number of advantages relative to conventional FOBT and is increasingly used relative to that test. This review summarizes current evidence for FIT in colorectal neoplasia detection and the comparative effectiveness of FIT relative to other commonly used CRC screening modalities. Based on evidence, guidance statements on FIT application were developed and quality metrics for program implementation proposed.

Stool testing for occult blood has long been recommended for colorectal cancer (CRC) screening in healthy adults.[1] This recommendation is based on randomized controlled trials showing short-term[2-4] and long-term[5,6] reductions in CRC incidence and mortality. These studies relied on the guaiac test as an indirect mechanism to detect blood in the stool. Such tests do not examine the stool for human hemoglobin, but rather are predicated on colorimetric detection of peroxidase activity. Specifically, human hemoglobin is a peroxidase catalyst when hydrogen peroxide is added to a guaiac-impregnated card. Unfortunately, many foods contain nonhemoglobin peroxidase activity, which confounds this test. Although guaiac-based CRC screening works, several factors limit its value,[7] as discussed later.

Fecal immunochemical tests (FITs) for CRC screening were developed as a direct measure of human hemoglobin in stool, using monoclonal or polyclonal antibodies against the globin moiety of human hemoglobin.[8,9] Most FITs are qualitative tests that visually indicate when hemoglobin is detected in the sample that is higher than a specific predetermined threshold. A few FITs are quantitative tests, whereby the amount of hemoglobin is measured numerically and then reported as positive if greater than a prespecified threshold. Although long-term, large, programmatic trials with FIT have not been completed yet, prospective data support the effectiveness of FIT as a screening tool, including some evidence that programmatic testing reduces CRC mortality.[10-12]

Although colonoscopy remains central to US-based CRC screening efforts,[13] to maximize compliance, effective community-based screening requires the availability of multiple screening modalities. FIT now is recognized as an important component of any CRC screening program.

This review has multiple purposes. First, to assist health care practitioners in the use of FIT, evidence is summarized about performance characteristics and the comparative effectiveness of FIT. Second, to assist practices or organizations developing FIT-based screening programs, evidence is summarized regarding its application (eg, number of tests and quantitative cut-off values for a positive test). Finally, additional sections of the review address important clinical questions regarding FIT. When possible, recommendations were made using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[14]

METHODS

Literature review

The committee relied on 2 previous systematic reviews of the FIT. The first was developed for the US Preventive Services Task Force,[15] and the second addressed the sensitivity of FIT for CRC.[16] To update this review, a search strategy similar to that used for the more recent review[16] was used to identify high-quality reports published since August 2013 through September 30, 2015. The updated review used the MEDLINE (Ovid) and Cochrane Database Search strategy as outlined by Lee et al[16] in their 2014

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publication. In addition, 2 authors (D.J.R. and J.K.L.) conducted specific literature searches to identify relevant reports for topics not directly dealing with the test characteristics of FIT and colorectal neoplasia detection. These identified reports then were reviewed and their citations were examined for further works informing the key study questions answered in the document. Although the literature search for the report was broad, the document was designed primarily to address US practice and focused on tests currently approved for use in the United States (Supplementary Table 1).

Definitions

When reporting quantitative hemoglobin measurements, we have followed recommendations by an expert panel and report the results or thresholds as micrograms of hemoglobin per gram of feces.[17] When needed, conversions from reports using nanograms of hemoglobin per milliliter of buffer were converted with the following formula: μg hemoglobin per g feces = (ng hemoglobin per mL × mL buffer)/(mg feces collected).

Process and levels of evidence

The United States Multi-Society Task Force (USMSTF) is composed of gastroenterologists with focused interest in colorectal cancer representing the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy. After the literature review, draft tables and the manuscript were completed and circulated to Task Force members. Guidance statements were developed through consensus obtained through multiple joint teleconferences. Once the final manuscript was complete, it was submitted for review and approval by all 3 gastroenterology societies.

The use of GRADE for USMSTF guidance reports has been outlined in detail elsewhere.[18] GRADE involves a comprehensive literature search and summary (often through meta-analysis), and then a separate review of literature quality and the development of recommendations. The USMSTF uses a modified qualitative approach based on literature review (as described earlier for this report), but without formal meta-analysis. GRADE allows for a separate assessment of the quality of the evidence and strength of recommendation. This approach explicitly recognizes the importance of literature in informing clinical recommendations, but allows latitude because recommendations may be influenced by other factors, such as patient preference and cost. Strong recommendations are those that would be chosen by most informed patients. Weak recommendations are those in which patient values and preferences might play a larger role than the quality of evidence. Within the document, we preface weak recommendations with phrases such as "we suggest," and strong recommendations with "we recommend."

EVIDENCE SUMMARY REGARDING FIT PERFORMANCE

Test characteristics for FIT when applied one time and programmatically

How sensitive and specific is FIT-based screening for CRC and advanced neoplasia with one-time application? Several cohort and cross-sectional studies analyzed the single-application test characteristics of FIT for CRC detection with or without a comparative guaiac-based fecal occult blood test (gFOBT), using colonoscopy or at least 2 years of follow-up evaluation as the reference standard[19-38] (Table 1). In a meta-analysis of 19 studies in asymptomatic average-risk adults the pooled sensitivity of FIT was 79% (95% confidence interval [CI], 0.69–0.86) for CRC, with a specificity of 94% (95% CI, 0.92–0.95).[16] Subgroup analysis that was restricted to studies in which only colonoscopy (and not clinical follow-up evaluation) was the reference standard found an overall sensitivity and specificity of 1-time FIT screening for CRC of 77% and 94%, respectively. A very large and recent US study completed after the meta-analysis examined the Food and Drug Administration (FDA)-cleared OC FIT CHEK (Polymedco, Cortland Manor, NY) in 9989 individuals undergoing colonoscopy. The reported sensitivity and specificity for cancer was 74% and 96%, respectively.[37]

Few studies compare FIT test characteristics of various brands with one another using cancer as the outcome. In the single comparative effectiveness study[21] of 2 FIT brands included in the meta-analysis,[16] the FDA approved OC-Sensor (Eiken Chemical Co, Tokyo, Japan) FIT had a higher sensitivity for CRC compared with the RIDASCREEN (R-Biopharm AG, Darmstadt, Germany) FIT (73.3% vs 60.0%, respectively), with similar specificities (95%). Importantly, the sensitivity of quantitative FIT assays can be adjusted by altering the threshold for a positive result. In the prior study, the OC-Sensor cut-off value was 6.1 μg/g vs a RIDASCREEN cut-off value of 24.5 μg/g. Presumably, the sensitivity of the latter test could be improved by reducing the threshold, although this would impact specificity negatively.

More recently, investigators using data from the Taiwanese national CRC screening program directly compared 2 FIT tests (OC-Sensor and HM-Jack [Kyowa Medex Co, Tokyo, Japan]) using the same threshold cut-off concentration used programmatically in that country (20 μg hemoglobin [hgb]/g feces). The OC-Sensor test had superior sensitivity for cancer relative to HM-Jack (80% vs 68%; $P = .005$), although no mortality benefit was observed over the 5-year study period.[11] A separate study compared 2 brands of FIT in a screening program in the Basque Autonomous Region in Spain.[39] Either OC-Sensor (20 μg hgb/g feces) or FOB Gold (Sentinel Diagnostics SpA, Milan, Italy) (20 μg hgb/g feces) was offered (varied by region) to nearly 38,000 individuals.

TABLE 1. Sensitivity and specificity of FIT for colorectal cancer in an average-risk population

Study, year	FIT brand	FIT samples	Cut-off value, μg/g	Cohort size	CRC, n	Reference standard[a]	Sensitivity	Specificity
Allison et al,[20] 1996	HemeSelect[b]	3	100	7493	35	2-year f/u	0.69	0.94
Itoh,[26] 1996	OC-Hemodia[b]	1	10	27,860	89	2-year f/u	0.87	0.95
Nakama et al,[31] 1996	Monohaem	1	20	3365	12	2-year f/u	0.83	0.96
Nakama et al,[32] 1999	Monohaem	1	20	4611	18	Colonoscopy	0.56	0.97
Cheng et al,[22] 2002	OC-Light	1	10	7411	16	Colonoscopy	0.88	0.91
Sohn et al,[36] 2005	OC-Hemodia[b]	1	20	3794	12	Colonoscopy	0.25	0.99
Morikawa et al,[30] 2005	Magstream HemSp	1	67	21,805	79	Colonoscopy	0.66	0.95
Launoy et al,[27] 2005	Magstream HemSp	2	67	7421	28	2-year f/u	0.86	0.94
Nakazato et al,[34] 2006	OC-Hemodia[b]	2	16	3090	19	Colonoscopy	0.53	0.87
Allison et al,[19] 2007	FlexSure OBT	3	300	5356	14	2-year f/u	0.86	0.97
Levi et al,[29] 2007	OC-Micro	3	15	80	3	Colonoscopy	0.67	0.83
Park et al,[33] 2010	OC-Micro	1	20	770	13	Colonoscopy	0.77	0.94
Parra-Blanco et al,[35] 2010	OC-Light	1	10	1756	14	2-year f/u	1.00	0.93
Levi et al,[28] 2011	OC-Micro	3	14	1204	6	2-year f/u	1.00	0.88
Chiang et al,[23] 2011	OC-Light	1	10	2796	28	Colonoscopy	0.96	0.87
de Wijkerslooth et al,[25] 2012	OC-Sensor	1	20	1256	8	Colonoscopy	0.75	0.95
Chiu et al,[24] 2013	OC-Light	1	10	8822	13	Colonoscopy	0.85	0.92
Brenner and Tao,[21] 2013	OC-Sensor	1	6.1	2235	15	Colonoscopy	0.73	0.96
Brenner and Tao,[21] 2013	Ridascreen[b]	1	24.5	2235	15	Colonoscopy	0.60	0.95
Imperiale et al,[37] 2014	OC-FIT CHEK	1	20	9899	65	Colonoscopy	0.74	0.96
Hernandez et al,[38] 2014	OC-Sensor	1	20	779	5	Colonoscopy	1.00	0.94

f/u, follow-up evaluation.
[a]Either a colonoscopy (detects CRC and adenomas) or a 2-year longitudinal follow-up evaluation using a cancer registry (only detects CRC) was used for FIT-negative patients.
[b]Discontinued or not available in the United States.

The participation rate was slightly higher with OC-Sensor (61.8% vs 59.1%; $P = .008$), but there was no significant difference in cancer detection among those who underwent colonoscopy for evaluation of a positive test (5.1% OC-Sensor vs 4.8% FOB Gold).

Reports of a single-application, 1-sample FIT showed sensitivity for advanced adenoma (defined as any adenoma ≥10 mm or with villous or high-grade dysplastic features) but varied from 6% to 56% in the screening population[21,24,25,29,30,33,34,36-38,40-42] (Table 2). This variation was owing to the different FIT brands used and the different cut-off values used to define a positive test. This was best shown in a German study comparing 5 different qualitative FIT brands (none of which were FDA approved or available in the United States).[42] By using colonoscopy as the gold standard, the sensitivities for advanced adenoma ranged from 25% to 56%, with specificities from 68% to 96% in 1319 average-risk subjects.

Varying cut-off levels to define a positive test result also affects FIT sensitivity and specificity for advanced adenomas. In a study of 1256 asymptomatic, average-risk Dutch subjects, the sensitivity of a 1-sample OC-Sensor FIT for advanced adenoma increased from 29% to 35%, with a corresponding decrease in specificity from 97% to 93% by decreasing the hemoglobin cut-off value from 20 to 10 μg/g.[25] Decreasing the cut-off value from 14 to 2 μg/g also increased the sensitivity of a one-sample RIDASCREEN FIT for advanced adenomas from 23.9% to 40.0%, with a corresponding decrease in specificity from 97.4% to 89.6% in 1319 asymptomatic, average-risk German subjects.[41]

The positive predictive value (PPV) of 1-time FIT for the detection of cancer and advanced adenoma has been determined across a range of populations (Table 3). The PPV is a function of both the inherent sensitivity of the test and disease prevalence in the population studied. The PPV of FIT for cancer ranged from 2.9% to 7.8% and for advanced neoplasia ranged from 33.9% to 54%. A positive FIT result significantly increased the yield of colonoscopy for these important outcomes relative to a screening colonoscopy, in which cancer (0.5%–1%) and advanced neoplasia (5%–10%) are detected much less frequently.[43,44]

How do FIT participation and performance characteristics for neoplasia detection change over multiple rounds of application? Available data indicate that FIT participation rates tend to remain stable through multiple rounds of screening.[45-52] For example, after 3

TABLE 2. Sensitivity and specificity of FIT for advanced adenoma in an average-risk population

Study, year	FIT brand	FIT samples	Cut-off value, μg/g	Cohort size	AA, n	Reference standard	Sensitivity	Specificity
Sohn et al,[36] 2005	OC-Hemodia[a]	1	20	3794	67	Colonoscopy	0.06	0.99
Morikawa et al,[30] 2005	Magstream	1	67	21,805	648	Colonoscopy	0.22	0.95
Nakazato et al,[34] 2006	OC-Hemodia[a]	2	16	3090	53	Colonoscopy	0.24	0.87
Levi et al,[29] 2007	OC-Micro	3	15	80	15	Colonoscopy	0.53	0.89
Graser et al,[40] 2009	FOB Gold[a]	1	2.4	265	24	Colonoscopy	0.29	0.85
Hundt et al,[42] 2009	Bionexia FOBplus[a]	1	2	1319	130	Colonoscopy	0.52	0.80
Hundt et al,[42] 2009	ImmoCARE-C[a]	1	30	1319	130	Colonoscopy	0.25	0.96
Hundt et al,[42] 2009	FOB advanced[a]	1	6	1319	130	Colonoscopy	0.27	0.91
Hundt et al,[42] 2009	QuickVue iFOB[a]	1	50	1319	130	Colonoscopy	0.56	0.68
Hundt et al,[42] 2009	PreventID CC[a]	1	2	1319	130	Colonoscopy	0.49	0.81
Haug et al,[41] 2010	Ridascreen[a]	1	14	1319	130	Colonoscopy	0.24	0.75
Park et al,[33] 2010	OC-Micro	1	20	770	59	Colonoscopy	0.24	0.94
de Wijkerslooth et al,[25] 2012	OC-Sensor	1	20	1256	119	Colonoscopy	0.29	0.97
Chiu et al,[24] 2013	OC-Light	1	10	8822	632	Colonoscopy	0.28	0.93
Brenner and Tao,[21] 2013	OC-Sensor	1	6.1	2235	207	Colonoscopy	0.22	0.97
Brenner and Tao,[21] 2013	Ridascreen[a]	1	24.5	2235	207	Colonoscopy	0.21	0.97
Imperiale et al,[37] 2014	OC-FIT CHEK	1	20	9899	760	Colonoscopy	0.24	0.94
Hernandez et al,[38] 2014	OC-Sensor	1	20	779	92	Colonoscopy	0.28	0.96

NOTE. Full list of FIT/FOBT device manufactures can be found in Supplementary Appendix.
AA, advanced adenoma.
[a]Discontinued or not available in the United States.

rounds of programmatic screening in The Netherlands, participation among those eligible to be screened remained greater than 60%.[47] After 4 rounds of a biennial screening program in Italy, 1862 individuals received all 4 invitations to be screened. Considering those individuals, 78% had attended at least once and 38% completed the FIT on all 4 occasions.[45] In a large annual FIT-based screening program at Kaiser Permanente Northern and Southern California, of the 670,841 individuals initially mailed a kit, 48% responded. Those initial responders who subsequently were eligible for screening and sent a kit continued to participate in the range of 75%–86% over the following 3 rounds.[52]

Similar to screening with gFOBT, the positivity rate, subsequent demand for colonoscopy, detection rate, and PPV for CRC decreased with successive rounds of screening with FIT[45-52] (Table 3). However, the detection rate and PPV for advanced neoplasia (ie, the combined outcome of cancer and advanced adenomas) remained higher with repeated FIT than with repeated gFOBT.[46] The decrease in positivity rates appeared to be owing to detection and removal of prevalent CRC and advanced adenomas in the first year, and the gradual culling of bleeding neoplasms. For example, in the study with the longest follow-up period,[45] no cancers were detected in the final (ie, fourth) screening round of this biennial FIT program. However, the PPV of FIT for advanced neoplasia remained high (ie, 30%–40%) throughout the 4 rounds of screening (Table 3).

Recommendation/summary

With 1-time application, FIT tests are approximately 80% sensitive for cancer detection and approximately 20%–30% sensitive for advanced neoplasia detection. To enhance advanced adenoma detection, repeated applications of FIT are required. Therefore, we recommend repeated testing (see later for details) to maximize the effectiveness of cancer detection and prevention with this modality. Individuals choosing FIT should understand the need for recurring testing and for colonoscopy to evaluate a positive FIT result. Programs to track cycles of testing are encouraged to facilitate completion. ***Strong recommendation; moderate-quality evidence***.

Given the high positive predictive value of FIT for cancer detection, colonoscopy is recommended when the test is positive, not repeat FIT. ***Strong recommendation; moderate-quality evidence.***

COMPARATIVE EFFECTIVENESS OF FIT-BASED SCREENING RELATIVE TO OTHER SCREENING MODALITIES

gFOBT vs FIT

Studies using different designs (eg, randomized controlled trial [RCT], cross-sectional) have compared gFOBT and FIT for the detection of neoplasia in screening populations (Table 4).[19-21,28,33,35,53-58] Significant variation

TABLE 3. FIT performance characteristics over multiple screening rounds in an average-risk population

Study, year	FIT brand (cut-off concentration)	Screening round	Participation rate, %	Positivity rate, %	Colonoscopy completion rate, %	PPV of CRC, %	PPV of advanced neoplasia, %
Denters et al,[46] 2012	OC Sensor (10 μg/g)	1	57.0	8.1	82[a]	6.0	54.0
		2	86.1	7.4	89	3.0	42.0
Parente et al,[49] 2013	HM-JACK (250 μg/g)	1	49.7	6.2	NR	4.0	32.9
		2	54.4	5.8	NR	3.0	33.3
van Roon et al,[51] 2013[b]	OC Sensor (10 μg/g)	1	61.0	8.6	94.5	7.8	33.9
		2	62.5	6.6	96.5	4.7	31.8
van Roon et al,[51] 2013[c]	OC Sensor (10 μg/g)	1	64.7	9.0	98.6	2.9	39.6
		2	63.2	5.4	98.6	1.4	35.7
Crotta et al,[45] 2012	OC Sensor (20 μg/g)	1	56.1	4.3	93.0	5.8	40.3
		2	62.3	4.2	89.5	1.9	33.4
		3	57.3	3.7	90.7	6.9	34.5
		4	62.5	4.4	94.1	0	33.3
Kapidzic et al,[47] 2014	OC Sensor (10 μg/g)	1	62.6	8.4	95.8	6.0	40.7
		2	63.2	6.0	97.0	3.1	33.2
		3	68.3	5.7	94.5	2.5	24.0
McNamara et al,[48] 2014	OC Sensor (20 μg/g)	1	50.7	10.1	81.5	4.0	NR
		2	47.5	8.0	82.4	1.2	NR
Stegeman et al,[50] 2015	OC Sensor (10 μg/g)	1	57.0	8.1	79.8	6.5	54.0
		2	56.0	7.9	83.9	3.8	41.7
		3	60.0	7.1	80.4	3.2	26.8
Jensen et al,[52] 2016	OC FIT-CHEK (20 μg/g)	1	48.2	5.0	75.5	3.4	NR
		2	75.3	3.9	80.5	2.1	NR
		3	83.4	3.7	80.5	2.3	NR
		4	86.1	4.3	81.1	2.1	NR

NR, not reported.
[a]Includes FOBT as well as FIT participants.
[b]Biennial FIT screening.
[c]Annual FIT screening.

exists across studies with the specific brands used (both gFOBT and FIT) and outcomes examined. Studies have indicated that FIT is superior to gFOBT in sensitivity for detecting CRC and advanced neoplasia, with comparable or only slightly reduced specificity.[19,21,33,35,54] A recently completed meta-analysis suggested that FIT was superior to gFOBT both for the detection of cancer (relative risk [RR], 1.96; 95% CI, 1.2–3.2) and advanced neoplasia (RR, 2.28; 95% CI, 1.68–3.10).[59]

Although the comparison studies used FITs with varying positivity rates, a recent German study showed that when the threshold level for a positive FIT was adjusted so that the positivity rates were similar for FIT (OC-Sensor) and gFOBT (HemOccult, Beckman Coulter, Krefeld, Germany), the sensitivity of FIT for CRC was 2 times higher than gFOBT (FIT sensitivity, 73.3%; gFOBT sensitivity, 33.3%), with similar specificities (>95%).[21] Similarly, in a French cancer screening program, 1-sample OC-Sensor (30 μg/g cut-off) had a true-positive detection rate for advanced neoplasia that was nearly twice that of Hemoccult II (9.7% vs 4.2%) at the same false-positive rate.[60]

In addition, participation is greater when individuals are offered FIT vs gFOBT. At least 4 RCTs showed improved adherence (an approximately 10% absolute increase), contributing to improved detection.[53,55,58,61] Adherence to screening with FIT vs gFOBT was summarized in 2 meta-analyses[59,62] and a separate review.[63] Both meta-analyses found participation to be approximately 20% greater for those offered FIT compared with gFOBT. Better adherence appears driven by simplifying the sampling method (fewer samples needed for FIT completion [usually 1 or 2 tests] compared with gFOBT [3 tests]), and removing the need for dietary and medication restriction with FIT (for more details on diet and medication, see later).

Stool DNA vs FIT. Stool DNA testing for colorectal cancer screening is predicated on the detection of DNA from shed neoplastic cells into the lumen of the

bowel with subsequent detection of mutant or epigenetically altered DNA markers. Over the past decade, buffers have been added to stabilize the DNA fragments and better markers have been chosen for the assay.[64] The most recent generation of the stool DNA test was compared directly with FIT (OC FIT-CHEK; Polymedco; 20 μg/g cut-off value) in approximately 10,000 asymptomatic individuals undergoing colonoscopy.[37] The multitarget stool DNA test now includes an immunochemical assay for human hemoglobin in addition to testing for DNA markers (methylated BMP3 and NDRG4 promoter regions, mutant KRAS, and β-actin). With 1-time testing, sensitivity for CRC was better with the multitarget stool DNA test (which essentially includes a FIT) relative to FIT alone both for cancer (92.3% vs 73.8%) and advanced lesions (42.4% vs 23.8%), but specificity was lower (86.6% vs 94.9%). Unlike prior studies, the trial provided direct information on the sensitivity of FIT and fecal DNA testing for large serrated class lesions. FIT sensitivity for sessile serrated polyps 1 cm or larger in size was 5%, compared with 42% for the multitarget stool DNA test. This FIT sensitivity was similar to the overall false-positive rate for the study, indicating that in this trial, FIT was ineffective in detecting sessile serrated polyps.

FIT vs sigmoidoscopy. Six studies compared the participation and yield of screening sigmoidoscopy and FIT (Table 5).[40,56,65-68] Three of the studies were randomized trials that examined both participation rates and yields.[56,65,66] In 1 trial, participation was better with FIT (61%) than flexible sigmoidoscopy [FS] (32%),[56] but participation was nearly identical in the other 2 studies.[65,66] In all 3 trials, advanced adenoma detection was superior with FS, but cancer detection was not significantly different.

One recent study reported the benefits of 1-time screening FS relative to FIT for proximal colon lesion detection.[68] The study simulated FS by using data derived from colonoscopy examinations completed as part of the ColonPrev trial (ClinicalTrials.gov number: NCT00906997) in Spain. Similar to the studies discussed earlier, overall advanced neoplasia detection was better in the FS-simulated group (6.3%) relative to the FIT arm (2.7%). However, the 2 modalities did not differ in advanced proximal neoplasia detection (odds ratio [OR] of FS vs FIT, 1.17; 95% CI, 0.78–1.76).

FIT vs colonoscopy. Three RCTs currently underway compare a screening strategy using total colonoscopy with FIT using an end point of CRC mortality.[69-71] One of the 3 studies (ColonPrev) reported an interim analysis after the first round of screening.[69] In that study, individuals were invited to either a screening colonoscopy (n = 26,703) or biennial FIT (n = 26,599) using the OC-Sensor device at a 15 μg/g cut-off level. Participation was higher in the FIT arm (34.2% vs 24.6%), with no difference in CRC detection. Advanced neoplasia detection was higher in individuals randomized to colonoscopy (1.9% vs 0.9%). Per-protocol analysis showed a trend toward improved cancer detection in individuals screened with colonoscopy relative to 1-time FIT (OR, 1.56; 95% CI, 0.93–2.56; $P = .09$). Because those in the FIT arm will continue to be screened biennially, additional cancers and adenomas will be detected. Thus, the long-term comparative effectiveness remains to be determined.

Other studies have compared FIT with colonoscopy (Table 6).[40,66,72] Most recently, Gupta et al[72] examined the participation and yield of no-cost FIT vs no-cost screening colonoscopy when inviting an uninsured US population that was not up to date with screening. Similar to the ColonPrev study, participation was higher with FIT (40.7% vs 24.6%) and no difference was observed in cancer detection between the 2 groups (0.4% vs 0.4%). Advanced neoplasia detection was superior with colonoscopy (1.3%) relative to a single application of FIT screening (0.8%).

Summary: comparative effectiveness

Adherence to FIT is superior to 3-card gFOBT and superior to colonoscopy in a non-US population and in an uninsured US population. FIT outperforms gFOBT in the detection of advanced neoplasia, and endoscopic strategies are superior to 1-time FIT for that outcome. A recent meta-analysis of studies largely performed outside the United States quantified many of these comparisons.[59] In that review, endoscopic strategies were associated with lower participation rates compared with FIT (RR, 0.67; 95% CI, 0.56–0.80), but there was a significantly higher advanced neoplasia detection rate (RR, 3.21; 95% CI, 2.38–4.32). FIT was superior to gFOBT both using the outcome of adherence (RR, 1.16; 95% CI, 1.03–1.30) and the detection of advanced neoplasia (RR, 2.28; 95% CI, 1.68–3.10).

These trials do not generally test a commonly used approach of offering screening in the United States called sequential testing. In the United States, most screening is opportunistic rather than programmatic. Clinicians often start the discussion of screening with an offer of colonoscopy, which is or should be followed by an offer of FIT if colonoscopy is declined. The process of offering 1 test (usually the test viewed as the most effective) and offering a second test to persons who decline the first is called *sequential testing*. Sequential testing beginning with sigmoidoscopy followed by fecal blood testing for persons declining sigmoidoscopy has resulted in improved participation rates ranging from 19% to 25% in 2 studies examining this approach.[73,74] Both studies showed enhanced advanced neoplasia detection including an increase in cancer detection of approximately 20%.

Recommendation/summary

When comparing FIT with gFOBT, FIT has improved sensitivity for CRC and advanced colorectal neoplasia detection at similar levels of specificity. There is RCT-level evidence that adherence is superior for

TABLE 4. FIT v gFOBT

Study	Design	gFOBT	FIT	Population
Allison et al,[20] 1996	Cohort that includes 2-year follow-up period	Hemoccult II Hemoccult Sensa (3 sample)	HemeSelect (3 sample) 100 μg/g cut-off	Screening (n = 8104)
Federici et al,[53] 2005	RCT	Hemo-Fec (3 sample)	OC-Hemodia (1 sample)	Screening (n = 7320)
Smith et al,[54] 2006	Paired, cross-sectional	Hemoccult Sensa (3 sample)	InSure (2 sample) 50 μg/g cut-off	Largely screening (total n = 2547)
Allison et al,[19] 2007	Cohort that includes 2-year follow-up period	Hemoccult Sensa (3 sample)	Flexure OBT (also known as Hemoccult ICT) (3 sample) 300 μg/g cut-off	Screening
Van Rossum,[55] 2008	RCT	Hemoccult II (3 sample)	OC-Sensor (1 sample) 20 μg/g cut-off	Screening adults (50–75); Dutch population gFOBT (n = 10,301) FIT (n = 10,322)
Hol et al,[56] 2010	RCT	Hemoccult II (3 sample)	OC-Sensor (1 sample) 20 μg/g cut-off	Screenees to 3 arms (FOBT, FIT, or FS) N = 15,011
Park et al,[33] 2010	Cross-sectional	Hemoccult II (3 sample)	OC-Sensa Micro (3 sample) 20 μg/g cut-off	Average-risk screenees (n = 770)
Parra Blanco et al,[35] 2010	Cohort	Hemofec (3 sample)	OC-Light (1 sample) 10 μg/g cut-off	Screening (n = 1756)
Levi et al,[28] 2011	RCT	Hemoccult Sensa (3 sample)	OC Micro (3 sample) 14 μg/g cut-off	Average-risk, age 50–75 y gFOBT, n = 7880 FIT, n = 4657
Wong et al,[57] 2012	Cohort	Hemoccult II	Hemoccult ICT 300 μg/g cut-off Magstream HemSp 67 μg/g cut-off	Screening colonoscopy program (1075)
Brenner and Tao,[21] 2013	Cross-sectional	HemOccult (1 sample)	RIDASCREEN (1 sample) 24.5 μg/g cut-off OC SENSOR (1 sample) 6.1 μg/g cut-off	Screening colonoscopy program (n = 2235)
Chubak et al,[58] 2013	RCT	Hemoccult Sensa (3 sample)	InSURE (2 sample) 50 μg/g cut-off OC-Auto (1 sample) 20 μg/g cut-off	Screening age, 50–74 y N = 2234
Raginel et al,[60] 2013	Cohort	Hemoccult II (3 sample)	Magstream (2 sample) 180 μg/g cut-off OC Sensor (2-sample) 30 μg/g cut-off	Screening age, 50–74 y N = 19,797

NPV, negative predictive value.

TABLE 4. Continued

Key findings	Conclusions
Sens/spec cancer Hemoccult II: 37.1/97.7 Sens/spec cancer Sensa: 79.4%/86.7% Sens/spec cancer HemeSelect: 68.8%/94.4%	FIT superior to Heme II in sensitivity to detect cancer
Participation FIT, 35.8% gFOBT, 30.4% Positive predictive value for advanced neoplasia favors FIT (29% vs 20%; $P = .2$)	Higher participation rates and positive predictive value of advanced neoplasia for FIT over gFOBT
Sensitivity when analysis was limited to patients who all had colonoscopy (irrespective of stool test) Sensitivity for cancer gFOBT, 37.5% FIT, 75% Sensitivity for "significant" adenoma FOBT, 15.2% FIT, 27.3%	FIT is superior to gFOBT in sensitivity for cancer and significant neoplasia
Sens/spec distal cancer gFOBT, 64.3%/90.1% FIT, 81.8%/96.9% Sens/spec distal advanced neoplasia gFOBT, 43.1%/90.7% FIT, 33.1%/97.5%	FIT has a higher sensitivity and specificity for left-sided cancer detection than gFOBT
Participation FIT, 59.6% gFOBT, 46.9% FIT significantly more likely to detect advanced neoplasia (1.4%) than gFOBT (0.6%)	Higher participation and detection rates with FIT over gFOBT
Participation FIT, 61.5% gFOBT, 49.5% FIT nonsignificantly more likely to detect cancer (1.8; 95% CI, 0.7–4.7) FIT significantly more likely to detect advanced neoplasia (2.0; 95% CI, 1.3–3.2)	Superior participation and detection with FIT over gFOBT
Sens/spec cancer gFOBT, 30.8%/92.4% FIT, 84.6%/89.8% Sens/spec advanced adenoma gFOBT, 13.6%/92.4% FIT, 33.9%/90.6%	Much better sensitivity and preserved specificity FIT relative to gFOBT
Sens/spec cancer gFOBT, 54.2%/96.9% FIT, 100%/92.7% Sens/spec advanced adenoma gFOBT, 19.8%/97.4% FIT, 56.8%/94.5%	FIT has a much higher sensitivity but slightly lower specificity for cancer and advanced adenoma compared with gFOBT
Participation FIT, 25.9% gFOBT, 28.8% Sens/spec cancer gFOBT, 61.5%/96.4% FIT, 100%/85.9%	FIT improved sensitivity despite lower compliance Specificity favors gFOBT
Sens/spec for advanced neoplasia Hemoccult II, 7.2%/98.8% Hemoccult ICT, 23.2%/95.8% Magstream, 37.7%/93.2%	FITS have higher sensitivity but reduced specificity for advanced neoplasia relative to gFOBT
At the same positivity rate (5%); positive predictive value and negative predictive value for advanced neoplasm superior for all FITS relative to HemOccult PPV, 17% vs 47%; 41%, 52% NPV, 90% vs 93%; 92%, 92%	FIT with well-defined cut-off values for test positivity show better test performance than gFOBT
Participation Sensa, 53.4% OC-Auto, 64% In Sure, 60% PPV for high-risk finding (CRC, advanced or multiple) Sensa, 29% PPV OC-Auto, 33% PPV In Sure, 24% PPV	The test with the fewest samples had highest uptake
At the same false-positive rate for Hemoccult II (0.98%), the true-positive rate for advanced neoplasia was significantly higher with each FIT Magstream (0.65%); OC sensor (0.90%) relative to FOBT (Hemoccult II, 0.42%)	Much better sensitivity and preserved specificity FIT relative to gFOBT for advanced neoplasia

TABLE 5. FIT vs FS

Study	Design	Sigmoidoscopy	FIT
Segnan et al,[65] 2005	RCT	FS	Immudia-Hem Sp, 1 sample, 100 μg/g cut-off
Segnan et al,[66] 2007	RCT	FS	Biennial Immudia-HemSp, 1 sample, 100 μg/g cut-off
Graser et al,[40] 2009	Prospective trial	Estimated by colonoscopy	FOB Gold, 1 stool sample sampled twice, 2.4 μg/g cut-off
Hol et al,[56] 2010	RCT	FS	OC-Sensor, 1 test, 20 μg/g cut-off
Khalid-de Bakker et al,[67] 2011	Cohort	Estimated by colonoscopy	OC-Sensor, 1 sample, 10 μg/g cut-off
Castells et al,[68] 2014	RCT	Estimated by colonoscopy	OC-Sensor, 1 sample, 15 μg/g cut-off

AN, advanced neoplasia; *colo*, colonoscopy; *GP*, general practitioner.
[a]This group included one-time FS and FS patients followed up with biennial FIT.

single-sample FIT compared with traditional 3-card gFOBT. Given these advantages, we recommend the use of FIT over gFOBT. ***Strong recommendation; high-quality evidence.***

PROGRAMMATIC CONSIDERATIONS

How many FIT kits/samples should be applied per cycle and at what interval?

Number of samples. The number of FIT samples needed for test completion (eg, from a single bowel movement vs multiple bowel movements across days) is an important consideration for optimizing CRC screening. In a Dutch study, van Roon et al[75] examined participation and clinical outcomes with 1 or 2 FITs (OC-Sensor, Eiken Chemical Co, Tokyo, Japan; cut-off value, 10 μg/g). There was no difference in participation, but 2-sample FIT was associated with a higher detection rate of advanced neoplasia (4.1% [95% CI, 3.3%–5.1%] vs 3.1% [95% CI, 2.5%–3.8%]).[75] In a Korean-based study examining the diagnostic accuracy of FIT with increasing FIT sample numbers, Park et al[33] showed that a 2-sample FIT (OC-SENSA MICRO; Eiken Chemical Co, Tokyo, Japan; cut-off value, 15 μg/g) had better sensitivity for CRC than a 1-sample FIT (92.3% vs 76.9%), with only a small decrease in specificity (91.4% vs 93.3%, respectively). However, if advanced adenoma was the target for screening, no difference under the receiver operator characteristic curve was seen for advanced neoplasia with more FIT samples, suggesting that a 1-sample FIT is equivalent for

TABLE 5. Continued

Population	Key findings	Conclusions
Average-risk screening FIT by mail (n = 2266) FIT by GP (n = 5893) 1-time FS (n = 3650)	Participation FIT/mail, 30.1% FIT/GP, 28.1% FS, 28.1% Advanced adenoma detection FIT, 1.5% FS, 5.3%[a] Cancer detection FIT, 0.34% FS, 0.35%	The advanced adenoma detection rate was 3× higher for FS
Average-risk screening FIT (n = 6075) FS (n = 6021)	Participation FIT, 32.3% FS, 32.3% Advanced adenoma detection FIT, 1.1% FS, 4.5% Cancer detection FIT, 0.1% FS, 0.6%	To detect 1 advanced neoplasm (ie, advanced adenoma or cancer), it would be necessary to invite 264 people with FIT, 60 with FS
Asymptomatic adults (n = 311)	Sens/spec for advanced neoplasia FS, 83.3%/59.6% FIT, 32%/85.8%	FS was more sensitive but less specific for AN than a 1-time FIT testing
Average-risk screening FIT (n = 4843) FS (n = 4700)	Participation FIT, 61.5% FS, 32.4% Advanced adenoma detection FIT, 2.0% FS, 7.4% Cancer detection FIT, 0.5% FS, 0.6%	Superior participation with FIT, higher diagnostic yield with FS driven by adenomas
Average-risk screening (n = 329)	Sens/spec for advanced adenomas FIT, 15.8%/96.9% FS, 73.7%/89.3%	FS was more sensitive for AN than FIT, caveat FS estimated by colo
Average-risk screening FIT (n = 10,507) FS (n = 5059)	Advanced neoplasia detection FIT, 2.7% FS, 6.3% Advanced proximal neoplasia detection FIT, 0.6% FS, 0.8%	FS was more sensitive for AN than FIT, but benefits only in left colon

the detection of advanced adenomas.[33] Likewise, investigators from Hong Kong,[76] France,[77] and Spain[38] found no advantage for a second kit for advanced neoplasia detection.

A meta-analysis also showed that the pooled performance characteristics of FIT for CRC were similar regardless of the number of FIT samples tested.[16] The pooled sensitivities for 1-, 2-, and 3-sample FIT for CRC were as follows: 0.79 (95% CI, 0.65–0.89), 0.77 (95% CI, 0.59–0.89), and 0.80 (95% CI, 0.66–0.89), respectively, in an asymptomatic, average-risk population.[16] The pooled specificities for 1-, 2-, and 3-sample FIT were as follows: 0.94 (95% CI, 0.92–0.95), 0.93 (95% CI, 0.90–0.95), and 0.93 (95% CI, 0.89–0.95), respectively.[16] Similarly, a cost-effectiveness analysis using the MIcrosimulation SCreening ANalysis (MISCAN)-Colon model examined 1- vs 2-sample FITs under a host of different screening assumptions (eg, hemoglobin thresholds, intervals).[78] Intensifying screening through shorter intervals between screening tests, for example, found 1-sample testing was more cost effective than 2-sample testing. The findings from the meta-analysis[16] and cost-effectiveness analysis[78] suggest that a simpler 1-sample FIT regimen provides similar results for CRC detection to more complicated multisample regimens, particularly if short intervals between screenings (ie, 1 year) are used.

Interval for repeat FIT screening. Programmatic screening with gFOBT performed annually decreases CRC-related mortality by up to 33%.[5] However, the optimal interval for CRC screening using FIT remains unclear. Presently, 2 ongoing RCTs are comparing colonoscopy

TABLE 6. FIT vs colonoscopy

Study	Design	FIT	Population	Key findings	Conclusion
Segnan et al,[66] 2007	RCT	Immudia-HemSp, 1 sample, 100 μg/g cut-off	Average-risk screening (age, 55–64 y) FIT (n = 6075) FS (n = 6021)	Participation FIT, 32.3% Colonoscopy, 26.5% Advanced adenoma detection FIT, 1.1% Colonoscopy, 6.3% Cancer detection FIT, 0.1% Colonoscopy, 0.8%	To detect 1 advanced neoplasm (AA or cancer), it would be necessary to invite 264 people with FIT, 53 with colonoscopy
Graser et al,[40] 2009	Prospective trial (segmental unblinding with CTC)	FOB Gold, 1 stool sample sampled twice, 2.4 μg/g cut-off	Asymptomatic adults (n = 311)	Sens/spec for advanced neoplasia Colonoscopy, 100%/43.0% FIT, 32%/85.8%	Colonoscopy is more sensitive for AN than a 1-time FIT testing
Quintero et al,[69] 2012	RCT	OC-Sensor, 1 sample, 15 μg/g cut-off	Average-risk screening FIT (n = 26,599) Colonoscopy (n = 26,703)	Screening participation FIT, 34.2% Colonoscopy, 24.6% Advanced adenoma detection FIT, 0.9% Colonoscopy, 1.9% Cancer detection FIT, 0.1% Colonoscopy, 0.1%	Superior participation with FIT; more advanced adenomas were detected in the colonoscopy group
Gupta et al,[72] 2013	RCT	OC FIT CHECK, 1 sample, 10 μg/g cut-off	Average risk; uninsured; not up to date with screening ages, 50–64 y Mailed no-cost FIT (n = 1593) Mailed invitation no-cost colonoscopy (n = 479) Usual care (n = 3898)	Screening participation FIT, 40.7% Colonoscopy, 24.6% Usual care, 12.1% Advanced adenoma detection FIT, 0.8% Colonoscopy, 1.3% Usual care, 0.4% Cancer detection FIT, 0.4% Colonoscopy, 0.4% Usual care, 0.2%	Mailed outreach improved screening, outreach was more effective with FIT

AA, advanced adenoma; *AN*, advanced neoplasia; *CTC*, computerized tomographic colonography.

with annual or biennial FIT screening for the risk of CRC incidence and mortality[69,70] and the results will not be available for at least another 10 years. However, in a cost-effectiveness analysis, Zauber et al[79] showed that a high-sensitivity fecal-based screening test (ie, FIT) performed annually yielded similar life-years gained compared with colonoscopy performed every 10 years. In the Dutch FIT-based screening program, the detection of advanced neoplasia was not influenced by the interval length when varied over 1 to 3 years.[51] As noted earlier, Goede et al[78] performed a cost-effectiveness analysis directly comparing 1-sample vs 2-sample FIT. Annual screening strategies were favored over multiple tests in a given cycle.

Recommendation

Based on currently available evidence, including the systematic reviews discussed earlier, the Task Force suggests a 1-sample annual FIT screening approach (Table 7). ***Weak recommendation; low-quality evidence.***

Is qualitative or quantitative FIT preferred for CRC screening and what hemoglobin threshold should be chosen?

Qualitative vs quantitative FIT. There are 2 types of FIT formats—qualitative and quantitative—that use different analytical techniques to detect human hemoglobin.[80] In general, qualitative FITs have a preset cut-off level for fecal hemoglobin concentration using lateral flow immunochromatographic analysis to determine FIT positivity. These qualitative FITs use similar technology adopted from many point-of-care tests for hormones and drugs. In contrast, quantitative FITs use immunoturbidimetric methods to measure fecal hemoglobin concentration and the cut-off fecal hemoglobin concentration for a positive test result can be adjusted by the end user. However, the FDA requires all quantitative FITs to be reported as positive or negative depending on the cut-off value for a positive test (reporting the fecal hemoglobin concentration is not permitted). Currently in the United States (Supplementary Table 1), the vast majority of FDA-cleared devices

TABLE 7. Summary of key recommendations regarding FIT application

Recommendation	Strength	Quality of Evidence
The Task Force suggests a one-sample annual FIT screening approach.	Weak	Low
The Task Force suggests that quantitative FITs be selected over qualitative FITs.	Weak	Low
The Task Force favors a lower threshold cut-off FIT (i.e., 20 μg/g or lower) to define a positive test	Weak	Low
When screening FIT is positive, colonoscopy is the recommended test for subsequent evaluation.	Strong	Moderate
In the absence of signs or symptoms of upper gastrointestinal pathology, a positive FIT and a negative colonoscopy should not prompt upper gastrointestinal evaluation.	Weak	Very low
Those with a positive FIT and a recent colonoscopy (i.e. before the individual would be due for repeat endoscopic examination) should generally be offered repeat colonoscopy.	Weak	Low
The Task Force recommends that, patients should be explicitly instructed that they do not need to adjust diet or medications to complete a FIT	Strong	Moderate
The Task Force suggests that FIT screening programs rely on spontaneously passed stool specimens and not an in-office DRE sample.	Weak	Very Low
Programs using FIT need not adjust distribution or mailing of FIT based on ambient temperature	Weak	Low
Programs using FIT should establish quality assurance practices to monitor key quality metrics. The committee suggests the following targets: • FIT completion rate to those offered testing of ≥60% • Proportion returning FIT that cannot be processed by lab of <5% • Colonoscopy completion rate for those with a positive FIT ≥80% • ADR >45% in men and >35% in women on colonoscopy exams to evaluate FIT positivity	Weak	Very Low

are qualitative tests, with only 2 quantitative systems available: the OC-Auto Micro 80 and the OC-Sensor Diana from Polymedoc (Cortland Manor, NY) and the i-Chroma system from Boditech (Chuncheon, South Korea).

In a meta-analysis of 4 qualitative and 4 quantitative FIT brands, the performance characteristics for CRC detection were similar.[16] The pooled sensitivity of quantitative FITs for CRC was 77% compared with 85% with qualitative FITs. Both FIT formats had a specificity of 94%. Two recent studies not included in the meta-analysis directly have compared the performance of a qualitative vs a quantitative FIT in the screening setting.[81,82] Both suggested improved detection with the quantitative FIT. In the first study,[81] although the positivity rate of the qualitative test was 3 times higher than the quantitative one (8.1% vs 2.5%), there was an improved positive predictive value for cancer with the quantitative test (14.4% vs 5.2%), which is predictable using a more-specific, less-sensitive test. The second study observed that the quantitative test has an improved positive predictive value relative to the qualitative test for both large adenomas and cancer.[82]

Qualitative FITs have other notable limitations. Interpreting the test as negative or positive may be more subjective than quantitative tests (such as the Polymedco OC-Auto Micro) that use automated reading.[83] Also, Hundt et al[42] showed that performance characteristics for advanced adenoma vary widely across FIT manufacturers when analyzing the same stool specimen, which cannot be attributed entirely to the different preset cut-off values used by each manufacturer. Moreover, in a US population-based screening study, Levy et al[84] discovered that 2 qualitative FITs (Clearview iFOB Complete [Alere, Orlando, FL] and OC-Light, [Polymedco, Cortland Manor, NY]) had quality-control issues; both FITs did not test positive at the preset cut-off value and one did not test positive at the lower limit of the manufacturer's stated sensitivity. One study evaluating 6 qualitative FIT tests observed that some tests used detection levels resulting in unacceptably low specificity for large-scale screening programs.[85] Thus, automated and well-studied quantitative FITs appear to have an advantage in consistency of performance characteristics for CRC and advanced adenomas, efficiency, and quality control. In addition, the ability of quantitative FITs to select and potentially adjust fecal hemoglobin cut-off concentrations to define a positive test allows the end user to meet endoscopic resource demands and select target clinical sensitivity or PPV for advanced neoplasia detection. For example, using data from those participating in a FIT-based program in Barcelona (n = 3109), investigators determined that those with a fecal hemoglobin concentration greater than 177 μg/g were nearly 4 times more likely to harbor advanced neoplasia than those with a fecal hemoglobin concentration below this level (OR, 3.80; 95% CI, 3.07–4.71).[86]

What should be the optimal cut-off value for a positive FIT test? Identifying an optimal cut-off value for defining a positive FIT result is crucial for any CRC screening program. This cut-off value influences both the number of cancers detected and the number of colonoscopies needed to follow-up these positive tests. In a meta-analysis, Lee et al[16] showed that varying the cut-off values used to define an abnormal test result influenced the performance characteristics of FIT for CRC. The sensitivity of 1-time screening FIT for CRC decreased with

increasing cut-off values, from 0.86 (95% CI, 0.75–0.92) using cut-off values less than 20 μg/g, to 0.67 (95% CI, 0.59–0.74) using cut-off values greater than 50 μg/g. Conversely, the specificity increased from 0.91 (95% CI, 0.89–0.93) to 0.96 (95% CI, 0.94–0.98). This trade-off in sensitivity and specificity with varying cut-off values also affects the accuracy of FIT for the detection of advanced neoplasms in screening populations.[25,29,41]

In the meta-analysis, the FIT cut-off value of less than 20 μg/g had the best combination of sensitivity and specificity for CRC compared with cut-off values ranging from 20 μg/g to 50 μg/g or greater.[16] However, colonoscopy resources are an important consideration when choosing a threshold for a positive FIT. Studies included in the meta-analysis using a 1-sample FIT with cut-off values less than 20 μg/g had positivity rates from 5.3% to 14.2%, which was higher compared with studies using a 1-sample FIT with cut-off values between 20 and 50 μg/g (positivity rates, 1.4%–7.5%). In a simulation modeling analysis using a quantitative FIT (OC-Sensor), Wilschut et al[87] compared many different cut-off strategies, ranging from 10 to 150 μg/g, and found that a cut-off value of 10 μg/g was the most efficient and cost-effective strategy for CRC screening, assuming a specificity of 95.8%. A study using the OC-Sensor Diana instrument in 14,289 Korean participants showed no significant difference in advanced neoplasia detection when comparing those undergoing testing with a threshold of 20 μg hgb/g feces (29.9%) vs a threshold of 10 μg hgb/g feces (30.8%).[88]

Based on these studies, a low cut-off (<20 μg/g) FIT offers the best performance characteristics (ie, combination of sensitivity, specificity, and overall diagnostic accuracy) for the detection of CRC while also being cost effective. However, selecting an optimal FIT cut-off value also should include factors such as the positivity rate, available colonoscopy resources, and the brand of FIT used.

Recommendations

Performance characteristics of quantitative and qualitative FITs for neoplasia appear generally similar. However, the Task Force suggests that quantitative FITs be selected over qualitative FITs. This recommendation is based on improved quality control with automated reading and the ability to adjust fecal hemoglobin cut-off concentrations to define a positive test. ***Weak recommendation; low-quality evidence.***

The optimal cut-off value for FIT should be determined by its performance characteristics, cost effectiveness, FIT device, and the screening program's available colonoscopy resources. Based on the limited evidence, the Task Force favors a lower threshold cut-off FIT (ie, ≤20 μg/g) to define a positive test. The decision to recommend use of FIT with a hemoglobin threshold including 20 μg/g (not just less than that threshold) reflects, in part, a practical consideration because that threshold currently is used by the commonly available quantitative test in the United States. ***Weak recommendation; low-quality evidence.***

When FIT is positive, what evaluation is recommended?

Screen-eligible individuals. In most cases, those with a positive FIT would be screen-eligible at the time the test result returns. As reviewed earlier, when FIT is positive, the PPV for significant neoplasia is high. Colonoscopy is the one structural examination that both directly evaluates the entire colorectal mucosa and affords the opportunity to simultaneously remove significant neoplasia. Given these characteristics, it is the optimal test to follow up on a positive screen and has been recommended previously by the Task Force for this indication.[89]

Computerized tomographic colonography and colon capsule endoscopy (CCE) are 2 other structural tests that have been evaluated in patients with a positive stool test.[90,91] A meta-analysis summarized 5 studies in which individuals were either gFOBT or FIT positive and underwent computerized tomographic colonography and a verification test (generally colonoscopy). Although sensitivity for adenomas 6 mm or larger was reasonably good (average, 89%; 95% CI, 84%–92%), specificity suffered (average, 75.4%; 95% CI, 59%–87%).[90] These results raise concerns that radiologists, knowing the higher prevalence of significant findings in patients testing positive on a stool-based test, err on over-reporting equivocal findings. Holleran et al[91] directly assessed CCE performance in 62 FIT-positive participants who agreed to undergo both CCE and colonoscopy. Although sensitivity for neoplasia detection was good (95%), specificity was not (65%). In addition, CCE provided a complete colon evaluation in just 73% of participants, with the remainder not having it reach the dentate line during the recording time.

Separate from the issue of which test to use to evaluate a positive FIT is whether subsequent testing is needed if the colon evaluation is unrevealing. Hemoglobin is degraded as it moves through the gastrointestinal tract and therefore FIT testing is viewed as specific for lower-tract bleeding. Therefore, the test would less likely be falsely positive in patients with upper-tract disease, such as severe esophagitis or gastritis. However, there are very limited clinical data evaluating this issue. In a single study in which FIT testing was applied simultaneously along with upper-tract imaging by barium meal, the gastric cancer detection rate was no different between patients with a positive FIT (0.15%) and patients with a negative FIT (0.13%).[92]

Individuals with a recent colonoscopy. Early repeat testing with gFOBT occurs frequently in practice despite a recent colonoscopy, presumably because of concerns of missed lesions and lesions with a more aggressive biology.[93] Because repeating gFOBT early can lead to subsequent unnecessary testing and higher health care costs, the Centers for Disease Control and multiple guidelines

recommend suspending gFOBT for at least 10 years after a normal colonoscopy.[94-96] This recommendation is based on expert opinion and the low positive predictive value of interval gFOBT for clinically significant colonic neoplasia.[93-96] One study found that only 1% of gFOBT-positive individuals were detected with an advanced neoplasm when they had a negative screening colonoscopy within the past 5 years.[93] Despite FIT's superior test performance characteristics compared with gFOBT, there are limited data to inform clinicians on the optimal approach to asymptomatic patients with a positive FIT who had a recent colonoscopy and are not due for repeat examination.

Prior studies have suggested that interval FIT testing is capable of detecting neoplasia in the high-risk adult population undergoing colonoscopic surveillance.[97,98] Bampton et al[97] reported that a first time FIT detected clinically significant neoplasia (defined as CRC, adenomas >10 mm, adenomas with villous or high-grade dysplastic features, or >3 adenomas of any size) in 1.8% of subjects who were enrolled in a colonoscopy-based surveillance program for either a personal or family history of colonic neoplasia. Lane et al[98] showed that interval FIT, in patients who had at least 2 prior colonoscopy examinations and with personal or family history of colonic neoplasia, detected 12 of 14 CRCs (86% sensitivity) and 60 of 96 (63% sensitivity) advanced adenomas during follow-up evaluation.

Recommendation/summary

When FIT is positive in screen-eligible individuals, colonoscopy is the recommended test for subsequent evaluation. ***Strong recommendation; moderate-quality evidence.***

The Task Force suggests that in the absence of iron-deficiency anemia or signs or symptoms of upper gastrointestinal pathology, a positive FIT and a negative colonoscopy should not prompt upper gastrointestinal evaluation. ***Weak recommendation; very low quality evidence.***

Given FIT's superior performance characteristics compared with gFOBT, the Task Force suggests that those with a positive FIT and a recent colonoscopy (ie, before the individual would be due for repeat endoscopic examination) generally should be offered repeat colonoscopy. Additional considerations for offering a colonoscopy include clinical context (eg, other worrisome signs, symptoms, or laboratory values), patient factors (eg, risk factors for advanced neoplasia, patient preferences), and prior colonoscopy examination quality (eg, poor bowel preparation, endoscopist's adenoma detection rate). ***Weak recommendation; low-quality evidence.***

Is dietary or medicine adjustment necessary with FIT?

One major limitation of gFOBT is a high false-positive rate related to dietary intake of foods with peroxidase activity. Equally worrisome is that dietary intake (eg, ascorbic acid) also can decrease test sensitivity systematically.[7] To overcome these limitations, screening participants restrict their diet during the period of testing and submit multiple stool samples (eg, generally 3 separate samples). Unlike gFOBT, FIT testing is not confounded by the dietary intake of foods with peroxidase activity.

Certain medications lower gFOBT specificity by facilitating bleeding from sources other than colorectal neoplasms. Limited data suggest that intake of aspirin, warfarin, and clopidogrel lower the positive predictive value of conventional gFOBT for advanced neoplasia detection.[99] In contrast, 2 high-quality prospective studies examining test characteristic in users of aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulants in patients receiving a FIT before screening colonoscopy suggest no negative impact on test characteristics.[100,101] In each case, sensitivity was improved for patients on antiplatelet therapy[100,101] or anticoagulant therapy,[100] with little decrease in specificity. Three studies examined the PPV of FIT in users of asprin[102,103] or anticoagulants[102,104] and found no evidence of diminished test performance comparing users with nonusers of these medications.

Recommendation/summary

There is no rationale to adjust diet or anticoagulation or antiplatelet agents when using FIT-based screening. The Task Force recommends that, to simplify testing and enhance adherence, patients should be instructed explicitly that they do not need to adjust diet or medications to complete a FIT test. ***Strong recommendation; moderate-quality evidence.***

Is a single in-office sample obtained on digital rectal examination acceptable?

Both the American Cancer Society and the United States Multi-Society Task Force on Colorectal Cancer recommend against using a digital rectal examination (DRE) during a clinical encounter for completion of gFOBT screening.[89] This recommendation reflects experience with gFOBT testing and the concern that individuals may be falsely reassured by a negative in-office test and will not complete the multiple gFOBT cards required for screening. In fact, evidence suggests that the sensitivity of in-office testing for advanced neoplasia and CRC detection is very low.[105]

The situation with FIT is different because a single stool sample can be used for screening. For some FIT kits, testing a stool sample obtained on DRE with the collection device would simply be impractical. Although it may be possible to test a DRE stool sample with some FIT devices, one study showed significantly different test performance when comparing results based on a passed stool sample vs a sample obtained on a DRE.[106] When comparing the 2 approaches in patients presenting for a medical check-up (n = 1688), the positivity rate when using the DRE sample was higher (5.4% vs 3.5% with a passed stool

sample), which translated into a significantly lower PPV for both adenomas and cancer using the DRE.

Summary/recommendation

There is limited information examining the test characteristics of FIT when applied to a stool specimen obtained by DRE. Available data suggest that test characteristics may suffer. The Task Force suggests that FIT screening programs rely on spontaneously passed stool specimens and not an in-office DRE sample. ***Weak recommendation; very low quality evidence.***

Should FIT screening be performed during warmer seasons?

Because the FIT process requires a stable hemoglobin molecule for a reliable test result, there are concerns about FIT performance when samples are returned during warm summer months. In an Italian population-based study, Grazzini et al[107] showed that an increase in temperature of 1°C reduced the probability of a positive FIT (OC-Sensor; cut-off value, 20 μg/g) by 0.7%, resulting in a 13% reduction in the probability of detecting advanced neoplasia during the summer compared with the winter season. Recently, van Roon et al[108] tracked FIT positivity rates according to calendar month and average outside temperature. In this study based in The Netherlands, a modest negative association was seen between outside temperature and FIT (OC-Sensor; cut-off value, 10 μg/g) positivity rates. An odds ratio of 0.97 (95% CI, 0.96–0.99) was found for FIT being positive with each degree in Celsius increase in average outside temperature.[108] In addition, positivity rates were significantly higher during the winter compared with the summer season (9.7% vs 8.0%, respectively; $P = .006$). However, this was not consistent across each of the summer months. Cha et al[109] examined the same issue within the Korean national screening program (n = 8316) using a 1-sample FIT (OC-Sensor Diana). When samples were completed at higher temperatures (≥25°C) compared with lower temperatures (<10°C), the hemoglobin concentration of the sample was significantly lower (0.25 vs 0.36 ng/mL hgb). However, the difference was relatively small and did not translate into a significant difference in the rates of positivity, adenoma detection, or advanced adenoma detection.[109] Chausserie et al[110] examined the impact of seasonal variation on FIT performance in a French screening program (OC-Sensor; positive cut-off value, 30 μg hgb/g feces). Positivity was lower in the summer months relative to other seasons (2.3% vs 3.0%; $P = .03$).

Recommendation/summary

Although limited data have indicated that ambient temperature affects test positivity, current evidence is insufficient to recommend against distributing or mailing FITs when outside temperatures are above a certain level. Programs using FIT should adhere closely to test manufacturer's specifications regarding storage and transport to minimize the effect of sample instability on FIT performance. ***Weak recommendation; low-quality evidence.***

Are FIT characteristics influenced by sample return time?

Sample stability over time is an important consideration with FIT because of the relative instability of the globin protein (relative to heme) in the collection systems used. Degradation of the sample is a particular concern for FITs that place fresh stool in a sample bottle including buffer. In fact, van Rossum et al[111] identified a decrease in sample positivity rates in those with a delay in processing of 5 or more days (positivity, 6%) relative to those processed without delay (8.7%). However, in a study based in The Netherlands, van Roon et al[108] found that FIT sample return times of up to 10 days did not decrease the positivity or detection rates of FIT. Similarly, in a report from the French screening program, processing delays of up to 10 days had no effect on positivity rates.[110] Efforts to improve stabilization buffers are ongoing and should further limit the impact of this factor on FIT-based programs.[112]

Summary/recommendation

There is no strong evidence that delays in FIT kit return of up to 10 days after sample deposit affects FIT performance. Nonetheless, the Task Force suggests that participants in FIT-based programs should be informed about the importance of rapid return of the kit (ie, preferably mailing it or returning it to the laboratory within 24 hours) once the sample has been deposited. Furthermore, programs should establish quality-assurance practices to monitor return times of the FIT kits and solicit repeat samples when kits fall outside the predetermined range of acceptability based on the device used (as established by the manufacturer). ***Weak recommendation; very low quality evidence.***

What are the key quality metrics to measure in a FIT-based program

Priority quality indicators for colonoscopy include cecal intubation rate, adenoma detection rate, and use of recommended surveillance intervals.[113] The success of any FIT-based program is predicated in part on the quality of colonoscopy performed for those who have positive tests.[114] However, this is just one element of a successful FIT-based program. Although some guidelines have been proposed for FIT-based programs,[115] significant work remains to be performed in this area.

Figure 1 outlines the key processes and potential opportunities for quality measurement in a FIT-based program. Once the target population for FIT screening is identified, the FIT needs to be delivered, completed, and returned for processing. FIT will be effective only when completed, and there is evidence that navigation tools can be helpful in this regard.[116] Upon receipt of the completed kit, the receiving laboratory

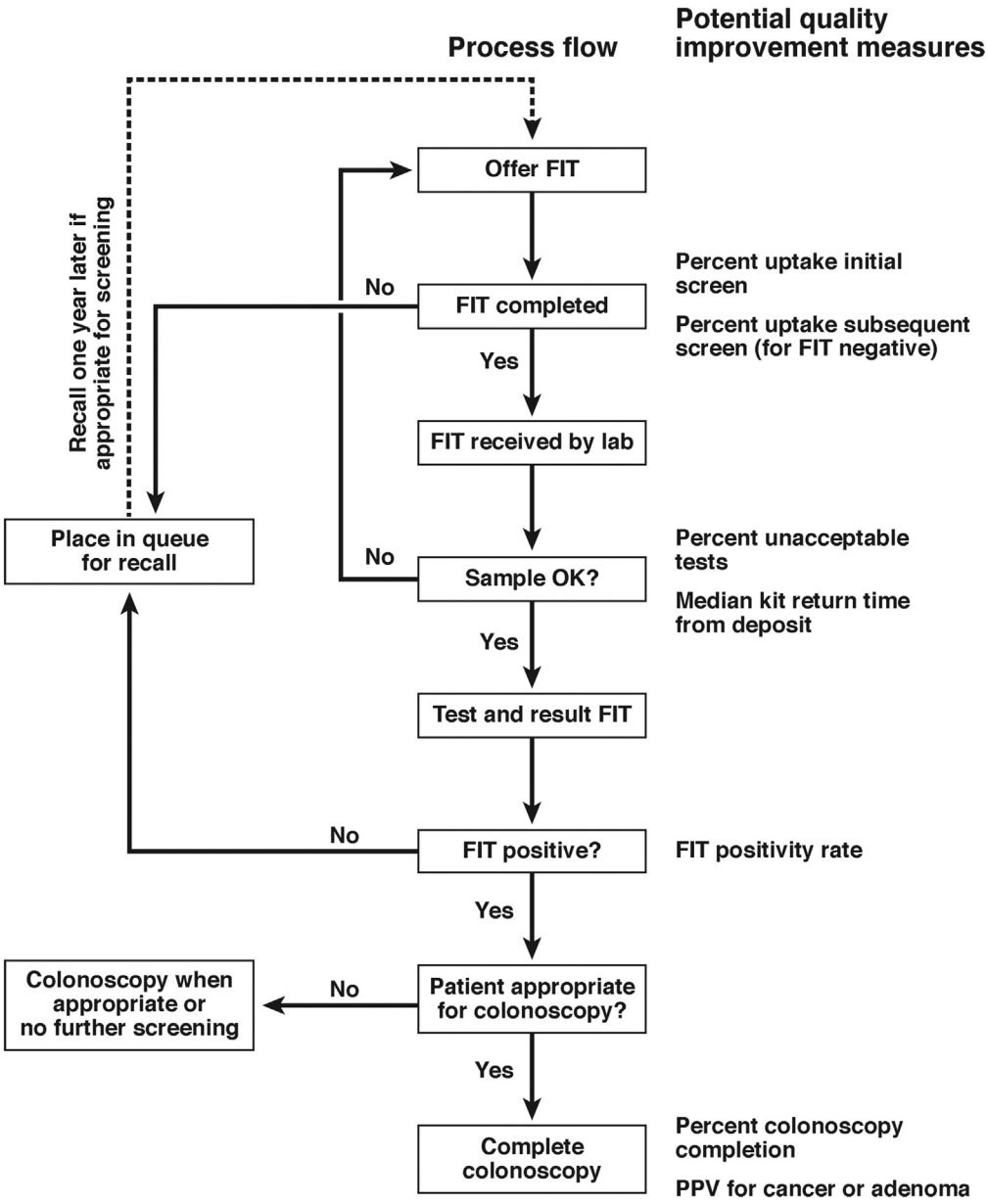

Figure 1. Key processes in FIT-based programs and opportunities for quality measurement.

should assess the suitability of the kit for testing (eg, not damaged or expired) and report the result according to the kit manufacturer's guidelines. Finally, the result needs to be delivered to the patient and when the test is positive, in most cases, colonoscopy completed. When the test on a given cycle is negative, systems should be in place to screen with FIT again in the following cycle (generally 1 year).

Few data are available to guide the development of quality benchmarks for FIT processes. Given the similarities to gFOBT-based programs, examining results from these programs may be informative. Ontario's ColonCancerCheck program reported that 29.8% of those eligible participated in screening, and when FOBT was positive, 74.6% proceeded to colonoscopy in 6 months.[117] Higher participation rates were reported from England (52%)[118] and Finland (70%).[119] The follow-up colonoscopy rate in Ontario also was lower than that reported in England (83%).[118] Table 3 shows similar metrics across a range of FIT-based programs that have reported results across multiple rounds of FIT-based testing. Participation rates of 60% appear consistent across rounds. In these studies, colonoscopy completion rates for those with a positive test are in the 80%–90% range. Rates of colonoscopy completion for those who are FIT positive were significantly higher in the Kaiser Permanente system relative to 2 other US-based health care systems.[120]

A more important measure of a FIT-based program is neoplasia detection. As reviewed earlier, establishing

benchmarks for CRC detection would be difficult for most centers given the relatively low likelihood of that finding and because the PPV for cancer decreases with subsequent rounds of testing. Establishing benchmarks for adenoma detection might be plausible. One challenge is that the PPV for adenoma does vary as the hemoglobin threshold for a positive test changes and with multiple rounds of testing (Supplementary Table 2). Generally, in most series, the PPV for any adenoma detection is greater than 45%. In the large, recently reported US experience at Kaiser (OC FIT Check; threshold, 20 μg/hgb), the PPV remained quite consistent across all 4 rounds of testing (47.4%–51.5%).[52] As expected, the positive predictive value for adenoma was higher in men (55%) than in women (42%).

Summary/recommendation

Similar to colonoscopy-based programs, FIT-based screening programs require careful attendance to quality assurance in provision of the test. Studies showing improved outcomes for selected measures in this area are needed. As this information is being developed, the committee suggests the following quality metrics for FIT-based testing programs:

- FIT completion rate to those offered testing of 60% or greater;
- Proportion returning FIT that cannot be processed by the laboratory of less than 5%;
- Colonoscopy completion rate for those with a positive FIT of 80% or greater;
- Adenoma detection rate greater than 45% in men and 35% in women on colonoscopy examinations performed to evaluate a FIT-positive test that uses a hemoglobin threshold of 20 μg/g or less. ***Weak recommendation; very low quality evidence.***

CONFLICTS OF INTEREST

These authors disclose the following: David A. Johnson is a clinical investigator for Exact Sciences and Epigenomics. David Lieberman served on scientific advisory Board for Exact Sciences. Douglas K. Rex received consulting fees from Olympus and research support from Endochoice. Douglas J. Robertson is on the scientific advisory board for Medtronic. Tonya Kaltenbach served as Consultant for Olympus America. The remaining authors disclose no conflicts.

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Abbreviations: CCE, colon capsule endoscopy; CI, confidence interval; CRC, colorectal cancer; DRE, digital rectal examination; FDA, Food and Drug Administration; FIT, fecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac-based fecal occult blood test; GRADE, Grading of Recommendations Assessment, Development and Evaluation; hgb, hemoglobin; OR, odds ratio; PPV, positive predictive value; RCT, randomized controlled trial; RR, relative risk; USMSTF, United States Multi-Society Task Force.

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SUPPLEMENTARY APPENDIX. Summary of FIT/FOBT device manufactures

Brand	Type	Manufacturer	Location
HemeSelect	FIT	SmithKline Diagnostics	San Jose, CA
OC-Hemodia	FIT	Eiken Chemical Co.	Tokyo, Japan
Monohaem	FIT	Nihon Pharmaceutical	Tokyo, Japan
Magstream HemSp	FIT	Fujirebio	Tokyo, Japan
FlexSure OBT	FIT	Beckman Coulter	Fullerton, CA
OC-Micro	FIT	Eiken Chemical Co.	Tokyo, Japan
OC-Light	FIT	Eiken Chemical Co	Tokyo, Japan
OC-Sensor	FIT	Eiken Chemical Co	Tokyo Japan
Ridascreen	FIT	R-Biopharm	Darmstadt, Germany
OC-FIT CHEK	FIT	Polymedco	Cortland Manor, NY
FOB Gold	FIT	Sentinel Diagnostics	Milan, Italy
Bionexia FOBplus	FIT	DIMA	Gottingen, Germany
ImmoCARE-C	FIT	CAREdiagnostica	Voerde, Germany
FOB advanced	FIT	Ulti med	Ahrensburg, Germany
QuickVue iFOB	FIT	Quidel	San Diego, CA
PreventID CC	FIT	Preventis	Bensheim, Germany
HM-Jack	FIT	Kiowa	Tokyo, Japan
InSure/Insure II	FIT	Enterix	North Ryde, NSW, Australia
Hemoccult ICT	FIT	Beckman Coulter	Fullerton, CA
Immudia-HemSp	FIT	Fujirebio	Tokyo, Japan
iChroma	FIT	Boditech	Chuncheon, South Korea
Hemosure	FIT	W.H.P.M Inc	Irwindale, CA
Hemoccult Sensa	FOBT	Beckman Coulter (formerly SmithKline Diagnostics)	Fullerton, CA
Hemofec	FOBT	Roche Diagnostics	Barcelona, Spain
Hemoccult II	FOBT	Beckman Coulter	Fullerton, CA
HemOccult	FOBT	Beckman Coulter	Krefeld, Germany

SUPPLEMENTARY TABLE 1. Summary of selected FIT devices cleared by the FDA for use

Brand(s)	Manufacturer/ distributor	FDA approval document	Sampling device	Number of samples	Qualitative or quantitative	Detection threshold
OC-Micro and OC-Sensor Test System	Eiken/Polymedco	K041408 K092330	Probe inserted into stool and then placed into collection vial	1 sample	Quantitative	Adjustable but set by manufacturer to 20 μg/g
i-Chroma iFOBT	Boditech	K132167	Probe inserted into stool and then placed into collection vial	1 sample	Quantitative	8 μg/g
Insure and Insure II	Enterix	K101831 K060930	Brush surface of stool and apply water from brushing to test card	2 sample	Qualitative	50 μg/g
QuickVue iFOB Test	Quidel	K021423	Probe inserted into stool and then placed into collection vial	1 sample	Qualitative	50 μg/g
Hemosure	W.H.P.M. Bioresearch and Technology, Inc	K041202	Probe inserted into stool and then placed into collection vial	1 or 2 samples	Qualitative	50 μg/g
OC-Light	Eiken Polymedco	K042197	Probe inserted into stool and then placed into collection vial	1 sample	Qualitative	10 μg/g
Clearview ULTRA FOB	Inverness Medical	K041297	Probe inserted into stool and then placed into collection vial	1 sample	Qualitative	50 μg/g
immoCARE	Care Diagnostics	K05298	Sample stool using the provided collection stick, then puts the collection stick back into the bottle of buffer solution	1 sample	Qualitative	30 μg/g
Consult IFOBT One Step+ Hema-screen SPECIFIC	Consult Henry Schien Immunostics	K060463	Collect sample with stick and place on card	2 sample	Qualitative	50 μg/g
Rapid FOBT Rapid Response Immuostics Rapid	CLIAwaived, Inc BTNX Teco	K061065	Insert the stick into the fecal specimen, wipe excess off, replace the stick in the tube	1 sample	Qualitative	6 μg/g
Forsure One Step Acutest Compliance Gold	Syntron Bioresearch Jant Pharmacal Germaine Lab	K063693	Insert applicator into stool, wipe excess off and screw applicator into tube	1 sample	Qualitative	50 μg/g
One Step FOBT	IND Diagnostics	K100031	Cylindric tube, vial dipstick sampling, developed on a cassette	1 sample	Qualitative	50 μg/g
Hemoccult ICT (also known as FlexSure OBT)	Beckman Coulter	K080812	Use stick to collect a pea-size stool sample and apply to top window and repeat process to bottom window	2- and 3-day screening kits	Qualitative	300 μg/g

SUPPLEMENTARY TABLE 2. FIT performance characteristics over multiple screening rounds in an average-risk population: PPV and adenoma

Study, year	FIT brand, cut-off	Screening round	Participation rate, %	Positivity rate, %	Colonoscopy completion rate, %	Positive predictive value for any adenoma, %
Denters et al,[46] 2012	OC Sensor, 10 μg/g	1	57.0	8.1	82[a]	76.3
		2	86.1	7.4	89	68.5
Parente et al,[49] 2013	HM-JACK, 250 μg/g	1	49.7	6.2	NR	36.6
		2	54.4	5.8	NR	37.7
Kapidzic et al,[47] 2014	OC Sensor, 10 μg/g	1	62.6	8.4	95.8	65.5
		2	63.2	6.0	97.0	52.1
		3	68.3	5.7	94.5	50.9
McNamara et al,[48] 2014	OC Sensor, 20 μg/g	1	50.7	10.1	81.5	36.7
		2	47.5	8.0	82.4	34.9
Jensen et al,[52] 2016	OC FIT Chek, 20 μg/g	1	48.2	5.0	75.5	51.5
		2	75.3	3.9	80.5	47.4
		3	83.4	3.7	80.5	48.5
		4	86.1	4.3	81.1	47.9

[a]Includes FOBT as well as FIT participants.