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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

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Abbreviations used in this paper: **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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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 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 $\times$ 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."

Table 1. Sensitivity and Specificity of FIT for Colorectal Cancer in an Average-Risk Population

Study, year	FIT brand	FIT samples	Cut-off value, $\mu g/g$	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.