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COLON/SMALL BOWEL

FIT: A Valuable but Underutilized Screening Test for Colorectal Cancer—It's Time for a Change

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Abstract: Although fecal immunochemical tests (FITs) have been used for colorectal cancer (CRC) screening in several countries for years, this has not been the case in the United States. The reasons for this are multifactorial, but if the United States hopes to increase screening rates, the evidence is in regarding FIT's benefits and potential. A publication in this issue of the *American Journal of Gastroenterology* provides "gold standard" evidence of its superiority over the standard guaiac test and opens opportunities for investigators to discover the most effective uses of this test for population screening.

Am J Gastroenterol 2010; 105:2026–2028; doi:10.1038/ajg.2010.181

Evidence that fecal immunochemical tests (FITs) are superior to guaiac tests (GTs) for colorectal cancer (CRC) screening began accumulating in the 1990's. English language publications were few and, in some, the studies were carried out in patients with known colorectal neoplasms or with symptoms and/or a personal or family history of colorectal neoplasm (1,2). Two studies were carried out comparing performance characteristics in an average-risk population and both showed FIT to be superior to GT (3,4). The increased cost of FIT compared with the standard GT and its low reimbursement lead to very little enthusiasm for its use in the United States, despite the fact that FIT was the screening fecal occult blood test of choice in Japan and its use had been shown to be cost-effective (5).

In 2002, the World Health Organization and the World Organization for Digestive Endoscopy concluded that fecal occult blood tests were effective in reducing the incidence and mortality of CRC, and that FITs removed the difficulties created by diet and drug restrictions. FITs were more amenable to standardized development and quality control than the GTs (6). In 2004, Centers for Medicare and Medicaid Services (CMS) concluded that adequate evidence existed to determine that FIT was an appropriate and effective CRC screening test for Medicare beneficiaries aged 50 years or older. The CMS reimbursement decision for FITs led many companies to submit their tests to the food and drug administration for approval, and the number of FITs available for use in the United States climbed dramatically.

Critics of the CMS determination emphasized that as the majority of FIT studies in average-risk populations did not have "gold standard" endoscopy results for FIT-negative patients, evidence of FIT's effectiveness was insufficient. One could argue that this evidence is unnecessary if the FIT is shown to uncover more cancers and advanced adenomas (AAs) than the GT in the same patient population. Several studies have proven so, including a recent one in the Netherlands (7). In 2005, this "gold standard evidence" began emerging (8,9). There is no longer any resistance to the idea that FITs' performance characteristics are superior to the standard GT. They are now one of the recommended screening tests in both the United States Preventive Services Taskforce Screening Guidelines for CRC and the American Cancer Society, US Multi-Society Task Force, and the American College of Radiology Guidelines (10,11). Nevertheless, a lot of important questions remain to be answered about FITs.

The most important issues pertaining to FITs that need clarification are the number of samples necessary for optimal sensitivity and specificity, the cutoff point for hemoglobin detection that provides the best sensitivity and specificity, the stability of stool samples, and the advantages, if any, of a quantitative FIT test over a qualitative test. Perhaps, the best study with gold standard evidence that answers many of these questions for one particular test is published in this issue of the *American Journal of Gastroenterology* (12). Park *et al.* present data on 770 average-risk patients undergoing screening colonoscopy who, before the procedure, provided three stool samples for testing by GT (Hemoccult II, Beckman Coulter, Brea, CA) and quantitative FIT (OC-Sensa Micro; Eiken Chemical, Tokyo, Japan) sold in the United States by Polymedco (Cortland Manor, NY). The results provide important information on the sensitivity, specificity, and positive and negative likelihood ratios of the Eiken FIT at different

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Received 2 February 2010; accepted 25 March 2010

thresholds of hemoglobin compared with the standard GT. The methods that the authors used provide an important quality standard for evaluation of any FIT. Results from this and similar studies in future will allow large healthcare organizations and individual providers to decide which FIT is best for their screening program. Up to one-third of AAs present were identified by the test. In a program of yearly screening, those missed can be identified long before they progress to fatal cancer. Removal of AA's allows for cancer prevention.

Tests of two stool specimens gave the best sensitivity and specificity for CRC, the primary target in a programmatic screening effort. These results mirror those in the earlier Japanese and Israeli studies (13,14). The number of specimens necessary for the best sensitivity and specificity are important because more tests can lead to improved sensitivity, but less compliance and specificity. In the Park *et al.* study, there was no difference under the receiver operator characteristic curve for advanced colorectal neoplasms (ACRNs), suggesting that one stool sample might be sufficient when AAs are the target. The high sensitivity for CRC (85%) and the observation that there were no differences under the receiver operator curves between one and three specimen testing for AA suggests the possibility that the number of specimens tested might be able to be decreased over the lifetime of the screened individual and the interval between screens lengthened.

The Park *et al.* study confirmed information from an earlier study (14) that the mean fecal hemoglobin value increases in a clinically important and statistically significant way, as the most advanced finding goes from normal colon to non-AA to AA to cancer. These observations prove that FITs are not a "nonspecific marker for screen relevant neoplasia" (15). Variations in hemoglobin levels per day were noted and provide an explanation for false-negative tests if ACRN's bleed intermittently or at different rates on different days.

The best sensitivity values in this study were found at a hemoglobin detection threshold of 75 ng/ml with a resulting high positivity rate of 12.2%. The positivity rate improved only slightly (11.2%) when the detection threshold was raised to 100 ng/ml. Nevertheless, at the manufacturer recommended threshold of 100 ng/ml, the number of colonoscopies needed to identify a patient with ACRN was only 2.7 compared with 5.1 with GT. The positivity rates are higher than those reported in other large screening programs using the same FIT. The most likely reason for this discrepancy is that Park *et al.* evaluated three FIT samples, whereas in other reported studies, only one sample was evaluated. In the Van Rossum study, a one-sample FIT at a cutoff of 100 ng/ml had a positivity rate of 5.5% (7). Other possible reasons for the different positivity rates include the fact that the Korean study entered patients from tertiary care centers, which might also account for the reported high number of cancers detected—13 in 770 average-risk patients. The positivity rate of GTs (7.7%) was also high, perhaps because in this Asian population, dietary restriction was not required.

A positivity rate that ranges between 5.5 and 12.2% means that a program using this particular FIT must have a have colonoscopy capacity to evaluate large number of positive cases. The results of the study highlight the usefulness of a quantitative FIT for allowing screening programs to determine which detection cutoff values they must use in order to have adequate capacity for colonoscopy evaluation of positive results, while still maintaining good sensitivity for ACRNs. For example, if one wanted to maintain the specificity seen with GT (92%), then the hemoglobin detection level of the FIT in this study would have to be set at ~125 ng/ml.

The issue of hemoglobin stability in the collected sample is very important because some FITs such as the Polymedco/Eiken product use wet sampling (specimens placed in a liquid buffer) and have the potential to perform poorly without refrigeration in warmer climates or where postal service is slow. In the Park *et al.* study, specimens were stored at 4 °C and developed within 2 weeks. Programs considering use of the Eiken FIT must determine how and whether the specimens need to be refrigerated. According to the manufacturer, degradation studies have shown that the sample is stable within the sampling bottle for 15 days at ambient temperature and for 30 days when refrigerated (package insert). More data is necessary for programs using this FIT to decide whether or not icing of specimens is necessary. Local conditions may also be helpful in deciding. Even FITs using dry sampling have different rates of decreasing hemoglobin detection over a 2-week period. According to the manufacturers of FITs using dry sampling, the sample is stable for 14 days at room temperature (20–32 °C) (InSure Quik FIT package insert, Enterix Inc., Quest Diagnostics Incorporated, Edison, NJ).

In this study, FIT seemed to be less sensitive at detecting AA in the distal vs. the proximal colon, but the authors point out that size of the lesion may be more important for detection than location. The ability of the monoclonal antibodies in any particular FIT to detect hemoglobin degradation products may determine its success in detecting advanced neoplasms in different parts of the colon. The FIT used and the target of its antibodies may determine the location where ACRNs are found most commonly; thus, in one study the FIT, FlexSure OBT (Beckman Coulter, Fullerton, CA) had better sensitivity for left-sided ACRNs than did the Magstream 1000 Heme SP (Fujirebio, Tokyo, Japan) (9).

Many gastroenterologists and their professional societies promote only one screening test as best, that is, colonoscopy. A recent review of CRC screening by primary care physicians shows how effectively the message has been communicated (16). Colonoscopy is now the most frequently recommended test and most physicians do not recommend the full menu of test options prescribed in national guidelines.

There have been consequences for taking this position and one of them has been that screening rates for CRC continue to lag well behind those for other cancers (17). As the "colonoscopy is best" recommendation was first made in the year 2000 (18), there has been a further decline in the use of other effective screening tests, particularly in the uninsured, underinsured, and underserved population (19,16). Even proponents of colonoscopy as the screening test of choice admit that protection against CRC by colonoscopy is imperfect (20,21). Others have wondered whether colonoscopy is a tarnished gold standard (22). Very few other countries have adopted a population screening program for CRC

using colonoscopy (23), and the soon to be published European Union CRC guidelines conclude that it is necessary to wait for the results of a randomized controlled trial before definite conclusions about the effectiveness of colonoscopy can be drawn (personal communication, Julietta Patnick, co-editor European CRC guidelines).

Transparency and evidence behooves gastroenterologists and their societies to encourage use of any and all of the evidence-based recommended screening tests in the United States Preventive Services Task Force CRC guidelines (10,24). Much more screening will be carried out if primary care providers and the American public are not made to feel that screening tests other than optical colonoscopy are ineffective.

A literature review reveals that with few exceptions, the best studies of FIT use come from countries other than the United States. This is problematic because some systematic reviews of evidence for policy decisions on screening exclude such studies. We must promote funding for the US studies to answer the many questions that we have about FITs and other screening tests that have proven efficacy. Reviewers and funders must be open to support studies examining all tests, both old established and new and promising (25). Despite the good work that has already been performed, many questions about FIT remain to be answered. Until we have better screening tests, the answers to these questions are urgently needed. Without a change in message and support for research to answer our questions, good screening tests will remain underutilized and more lives lost to a preventable and curable disease.

CONFLICT OF INTEREST

Guarantor of the article: James E. Allison, MD.

Specific author contributions: James E. Allison wrote this article.

Financial support: None.

Potential competing interests: James E. Allison has been an *ad hoc* consultant to Quidel Corporation, San Diego. He has agreed to give a webinar on screening tests for colon cancer for Beckman Coulter Corporation in March 2010. He is on the Scientific Advisory Board of IntelligeneScan Corporation. It does not have any screening test for CRC on the market.

REFERENCES

1. St John DJB, Young GP, Alexeyeff MA *et al.* Evaluation of new occult blood tests for detection of colorectal neoplasia. Gastroenterology 1993;104:1661–8.
2. Petrelli N, Michalek AM, Freedman A *et al.* Immunochemical versus guaiac occult blood stool tests: results of a community-based screening program. Surg Oncol 1994;3:27–36.
3. Allison JE, Tekawa IS, Ransom LJ *et al.* A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996;334:155–9.
4. Robinson MHE, Marks CG, Farrands PA *et al.* Population screening for colorectal cancer: comparison between guaiac and immunological fecal occult blood tests. Br J Surg 1994;81:448–51.
5. Shimbo T, Glick HA, Eisenberg JM. Cost-effectiveness analysis of strategies for colorectal cancer screening in Japan. Int J Technol Assess Health Care 1994;10:359–75.
6. Young GP, St John DJ, Winawer SJ *et al.* Choice of fecal occult blood tests for colorectal cancer screening: recommendations based on performance characteristics in population studies: a WHO (World Health Organization) and OMED (World Organization for Digestive Endoscopy) report. Am J Gastroenterol 2002;97:2499–507.
7. Van Rossum LG, Van Rijn AF, Laheij RJ *et al.* Random comparison of guaiac and fecal immunochemical blood tests for colorectal cancer in a screening population. Gastroenterology 2008;135:82–90.
8. Morikawa T, Kato J, Yamaji Y *et al.* A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;125:422–8.
9. Allison JE, Sakoda LC, Levin TR *et al.* Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007;99:1–9.
10. US Preventive Services Taskforce. US Preventive services taskforce screening for colorectal cancer: US preventive services taskforce recommendation statement. Ann Intern Med 2008;149:627–47.
11. Levin B, Lieberman DA, McFarland B *et al.* Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force On Colorectal Cancer, and the American College Of Radiology. Gastroenterology 2008;134:1570–95.
12. Park D, Ryu S, Kim Y *et al.* Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average-risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105: 2017–25 (this issue).
13. Nakama H, Kamijo N, Fujimori K *et al.* Relationship between fecal sampling times and sensitivity and specificity of immunochemical fecal occult blood tests for colorectal cancer: a comparative study. Dis Colon Rectum 1997;40:781–4.
14. Levi Z, Rozen P, Hazazi R *et al.* A quantitative immunochemical fecal occult blood test for colorectal Neoplasia. Ann Intern Med 2007;146:244–55.
15. Osborn NK, Ahlquist DH. Stool screening for colorectal cancer; molecular approaches. Gastroenterology 2005;128:192–206.
16. Klabunde CN, Lanier D, Nadel MR *et al.* Colorectal cancer screening by primary care physicians recommendations and practices, 2006-7. Am J Prev Med 2009;37:8–16.
17. NCI. Cancer bulletin. August 21, 2007;4:24.
18. Rex DK, Johnson DA, Lieberman DA *et al.* Colorectal cancer prevention 2000: screening recommendations of the American College of Gastroenterology. Am J Gastroenterol 2000;95:868–77.
19. Shapiro JA, Seeff LC, Thompson TD *et al.* Colorectal cancer test use from the 2005 National Health Interview Survey. Cancer Epidemiol Biomarkers Prev 2008;17:1623–30.
20. Lieberman D. Colonoscopy: as good as gold? Ann Intern Med 2004;141:401–3.
21. Rex D, Eid E. Considerations regarding the present and future roles of colonoscopy in colorectal cancer prevention. Clin Gastroenterol Hepatol 2008;6:506–14.
22. Cooper GS. Colonoscopy: a tarnished gold standard? Gastroenterology 2007;132:2588–604.
23. Benson VX, Patnick J, Davies AK *et al.* Colorectal cancer screening: a comparison of 35 initiatives in 17 countries. Int J Cancer 2008;122:1357–67.
24. Allison JE. Colorectal cancer screening guidelines: the importance of evidence and transparency. Gastroenterology 2010; 138:1648–52.e2.
25. Allison JE. The imperative of equal funding for studies that evaluate any of the evidence-based, guideline-recommended colorectal cancer screening tests editorial. Clin Gastroenterol Hepatol 2009;7:1269–71.