Why What You May Not Know About Fecal Immunochemical Testing Matters

Some U.S. primary care physicians and many of their patients may be unaware that fecal immunochemical tests (FITs) are noninvasive, easy to prepare, and inexpensive and have effectiveness similar to that of colonoscopy when used in a consistent, programmatic fashion to screen for colorectal cancer (CRC) (1). The paucity of studies comparing FITs and colonoscopy in 2000 may have been why Podolsky advocated for insurers to cover colonoscopic screening in all average-risk persons aged 50 years or older (2). Shortly thereafter, Congress ordered Medicare to cover the procedure without requiring published evidence of its superiority over less invasive and cheaper tests. In 2019, although trials are under way, we still lack published results of randomized controlled trials showing that colonoscopy is superior to FITs.

Currently, only about 65% of U.S. adults aged 50 to 75 years have been screened for CRC, and most of them have been screened with colonoscopy (3). Uninsured, underinsured, and poor persons are disproportionately represented in the unscreened group. Better education to inform patients and physicians that regular screening with FITs is not a "second-best" strategy or less than a "gold standard" strategy for average-risk persons could help the United States reach its Healthy People 2020 goal of screening 80% of eligible adults. Strong evidence and messaging are necessary to change the preference for colonoscopic screening in the United States, though preliminary data indicate that when offered a FIT, people are likely to choose it over colonoscopy (4).

The systematic review by Imperiale and colleagues in this issue may help to reassure physicians and patients about the performance of FITs for CRC detection (5). Using 31 studies involving 120 255 patients, they concluded that single-application FITs have moderate to high sensitivity and specificity for CRC, depending on the positivity threshold. The sensitivity (1-time testing only) for advanced adenomas was lower than for CRC, regardless of the threshold; however, even "advanced" adenomatous polyps are not cancerous, and most never progress to cancer. In a program of repeated FIT screenings (programmatic screening), the likelihood of detection of advanced adenomas is high even when a FIT with low single-application sensitivity is used. A modeling study by Knudsen and colleagues suggests that FITs can also reduce CRC incidence if used consistently over time (6).

It should be reassuring to skeptics that most countries with CRC population screening programs use FITs as their test of choice. For example, in Canada, a positive FIT result is mandatory in an average-risk patient before colonoscopy is covered by insurance. Further, the 2017 guidelines from the U.S. Multi-Society Task Force on Colorectal Cancer recommended colonoscopy every 10 years or annual FIT as first-tier options for screening for colorectal neoplasia in average-risk persons (strong recommendation; moderate-quality evidence) (7), a substantial, helpful, and important difference from its 2008 recommendations (8).

The decision about which FIT to use in programmatic screening is critical. Fecal immunochemical tests are immunoassays that are specific for human hemoglobin, forming an antibody-antigen complex with its globin protein moiety. Because different FITs have antibodies to different epitopes of globin, different collection and preservative techniques, different numbers of required samples, and different hemoglobin cutoffs for a positive result, they cannot be considered or evaluated as a single class of test.

Fecal immunochemical tests come in 2 forms: qualitative and quantitative. Qualitative FITs are reported as positive or negative on the basis of the hemoglobin cutoff determined by the manufacturer and are designed as point-of-care tests. Quantitative FITs measure the concentration of hemoglobin in a fecal sample, and a positive result is determined by those in charge of the screening program on the basis of the known correlation of the results with the presence of advanced colonic neoplasms at that objectively set cutoff.

Qualitative FITs are categorized by the U.S. Food and Drug Administration (FDA) as "simple laboratory examinations and procedures that have an insignificant risk of an erroneous result" and are therefore waived from the requirements of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories with a CLIA waiver are not subject to routine inspection. The FDA's approval of FITs as simple tests for blood rather than for advanced colorectal neoplasms has allowed for clearance of low-performing tests. Because FITs are used to screen for CRC worldwide, the standards for U.S. approval should be higher than they are. The FDA has "cleared" but has not "approved" many CLIA-waived qualitative FITs, including some that are sold over the counter, but has yet to approve any quantitative FIT for use in the United States. One quantitative FIT, the OC-Sensor (Eiken Chemical), is widely used in the United States but was developed and approved and is interpreted as a qualitative test. As of 11 July 2017, the CLIA test categorization database included 134 test systems for occult blood in feces, 5 qualitative automated FITs, and 129 waived nonautomated FITs. However, high-quality studies comparing different FITs for detection of CRC, overall and by stage, are lacking (9, 10).

Physicians in the United States must understand the advantages of FITs as screening tests for CRC and educate and advocate to increase screening rates,

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especially in vulnerable populations. If we hope to achieve national goals for CRC screening, we must learn as much as we can about the screening tests and advocate for funding of comparative studies of available tests and insurance coverage not only for screening colonoscopies but for those done after a positive FIT result.

James Allison, MD
University of California, San Francisco, San Francisco, California, and Kaiser Permanente Northern California Division of Research
Oakland, California

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Corresponding Author: James Allison, MD, Division of Gastroenterology, Department of Medicine, University of California, San Francisco, 1001 Potrero Avenue, Room 3D, San Francisco, CA 94110; e-mail, james.allison@ucsf.edu.

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