

Newer Fecal Tests: Opportunities for Professionals in Laboratory Medicine

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There are differences in practice between the US, Europe, and other countries in screening for colorectal neoplasia (1) and investigation of other common lower gastrointestinal tract problems. Colonoscopy is often considered the gold standard for detection of colorectal neoplasia, and deaths from colorectal cancer can undoubtedly be reduced through removal of adenomatous polyps (2, 3). Colonoscopy is a scarce resource in many countries, however, and it may be limited to those with comprehensive health insurance. Consequently, there is much interest in using fecal tests to decide who will truly benefit from colonoscopy, particularly because the symptoms reported for colorectal diseases overlap considerably, making clinical decision-making about whom to refer difficult.

In this issue of the Journal, Kok and colleagues (4) report a study on the diagnostic accuracy of point-of-care tests (POCTs)⁶ for fecal calprotectin and occult blood in primary care and assessing what they term “organic bowel disease.” A qualitative immunochemical fecal occult blood test was used. We have recommended (5) that tests that use antibodies to detect fecal hemoglobin be termed “fecal immunochemical tests for hemoglobin” and that the abbreviation “FIT” be used, because guaiac-based fecal occult blood tests (gFOBTs) and FITs are very different tests. As the authors mention, FITs are rapidly superseding traditional gFOBTs because of their many advantages, including that only a single sample is generally collected, the available collection devices encourage adoption of the test, the test is more specific for lower gastrointestinal

bleeding, and dietary restriction is definitely not required. Indeed, the many disadvantages of gFOBTs with respect to sample collection and handling, analysis, and interpretation of results (6) have led to the general consensus that their use is obsolete because of the much better performance characteristics of FITs. We strongly advocate that professionals in laboratory medicine (PLMs) encourage current users of gFOBTs in laboratories, clinics, wards, and primary care to replace these tests with the more effective FITs.

Kok and colleagues (4) performed fecal tests on samples from patients with lower-abdominal symptoms. The authors performed diagnostic endoscopic and histologic examinations and reported comprehensive estimates of clinical characteristics. STARD (Standards for Reporting of Diagnostic Accuracy) guidelines (7) were followed. We advocate that, whenever possible, PLMs should participate with clinical colleagues in studies of diagnostic accuracy and encourage adherence to these guidelines. The work of Kok and colleagues builds on previous studies of fecal calprotectin, which have amply demonstrated this marker to be useful in differential diagnosis and to be potentially useful in clinical management (8). Moreover, the available data support the view that the lack of a detectable calprotectin concentration in a low-risk patient supports the discharge of the patient without further invasive investigation. Much less work has been reported on the use of either a gFOBT or FIT in assessing symptomatic individuals; however, the report on a recent meta-analysis (9) stated that, although combinations of patient symptoms and FIT results showed good diagnostic performance for colorectal cancer, the evidence from primary care was lacking. We strongly support the view expressed that high-quality studies on the role of these tests in the diagnostic investigation of colorectal cancer in primary care are urgently needed. We believe that PLMs should play a pivotal role in the planning and execution of such studies.

The diagnostic accuracy of the tests, alone or in combination, was low when all adenomas, irrespective of size, were considered as serious colorectal disease. In consequence, Kok and colleagues (4) rightly considered that the tests were not very useful for ruling in, largely because calprotectin is a general protein marker of gut damage and has even been suggested to be of value in colorectal cancer screening (8). Conversely,

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⁶ Nonstandard abbreviations: POCT, point-of-care test; FIT, fecal immunochemical test for hemoglobin; gFOBT, guaiac-based fecal occult blood test; PLM, professional in laboratory medicine; STARD, Standards for Reporting of Diagnostic Accuracy.

the negative predictive values, a major determinant of clinical utility in this primary-care setting, were >90%. Thus, the ability to identify a large population for which the presence of colorectal disease could be ruled out to a reasonable extent was evident, not only for each test taken individually but even more so when the 2 POCTs were combined. Thus, a strategy that might be adopted in primary care would be to perform calprotectin and FIT analyses on presentation and then refrain from referral for colonoscopy if both of the results were negative. This strategy is appealing because it cuts down on the number of inappropriate referrals, but if referrals had been based on only the combined results of the 2 tests used in this particular study, some cases, predominantly adenoma, would have been missed. Although most polyps will never become cancer and most people die with, and not from, polyps, it is of concern that 5% of the patients with colorectal cancer and 10% of the patients with inflammatory bowel disease would have been missed.

A very important follow-up question is whether this approach could be improved, because it is clinically important to detect most colorectal disease and, ideally, never to miss colorectal neoplasia or other serious disease. Kok and colleagues (4) used qualitative POCTs for both calprotectin and FIT. These tests are generally based on immunochromatographic test cassettes and have advantages in that they are relatively inexpensive, are easy to perform, and usually have a built-in positive control. Thus, they might be considered most suitable for use in primary care. The performance obtained with POCTs is often inferior to that obtained in laboratories, however, and there are many prerequisites to ensure adequate performance in the POC setting (6). Moreover, POCTs have a number of telling disadvantages, including that the cutpoint concentrations between negative and positive results are set by the manufacturers of the devices and cannot be adjusted. It is vital to recognize that the cutpoint concentrations for available calprotectin tests (8) and FITs (5) differ substantially. Different cutpoint concentrations will lead to different clinical performance characteristics, and thus the work of Kok and colleagues (4) may not be transferable over time and geography if other tests are used. Positivity rates will increase as the cutpoint concentration decreases, whereas sensitivity will increase and specificity will decrease. Moreover, although fecal calprotectin has been reported to be reasonably stable (8), the hemoglobin in passed feces is not, and it is essential for samples to be directly collected onto or into the collection devices. Sampling into the traditional fecal pots and delay before analysis will lead to false-negative results and to missing serious disease (6). The selection of the tests appropriate for the clinical purpose and the ways in which these tests

are used—from sample collection to the reporting of results—could be facilitated by the involvement of PLMs.

There have been many studies on the use of FIT methods in screening of the asymptomatic population, and the plethora of lessons learned can be applied for the potential use of such tests in the symptomatic population. Many structured screening programs currently use automated immunoturbidimetry tests available from several manufacturers to quantitatively estimate the fecal hemoglobin concentration (10). Quantitative techniques for measuring calprotectin, such as the ELISA used by Kok and colleagues (4), are also available (8), although the development of additional automated analytical techniques would be of considerable value. Existing analytical systems for FITs have many advantages (6, 10), including higher throughput and enhanced quality, while eliminating the potential for visual bias by observers. The most telling advantage is that the user can select the cutpoint concentration used to trigger further investigation, usually colonoscopy. Importantly, recent work (11) has confirmed that fecal hemoglobin concentrations are very dependent on sex and age, and it is possible that different cutpoint concentrations would be appropriate for different groups, just as partitioned reference intervals are used for other analytes. Moreover, the risk of neoplasia increases as the fecal hemoglobin concentration increases (12), which has ramifications for decision-making regarding the ideal cutpoint concentration to use for a particular application. Furthermore, there is a growing interest in risk-scoring algorithms for asymptomatic individuals, one of which now incorporates fecal hemoglobin concentration (13). For symptomatic patients (14), such algorithms might well benefit from incorporation of the fecal hemoglobin concentration and, possibly, the fecal calprotectin concentration as well.

Kok and colleagues (4) have demonstrated that a combination of a calprotectin assay and a FIT might be beneficial in the direction of colonoscopy for the patients who would benefit the most. Further evolution of these concepts requires that considerable effort be expended, not only on further research and development, particularly with automated analytical systems, but also on the standardization of a number of aspects of FIT methods. The ongoing effort through the Expert Working Group on Fecal Immunochemical Tests for Hemoglobin of the Colorectal Cancer Screening Committee of the World Endoscopy Organization (5) would benefit further from the expertise of PLMs.

Finally, the editors of laboratory medicine journals recently published an appeal to medical journal editors on the need for full descriptions of laboratory methods and specimen handling in reports of clinical

studies (15). Many of the recent publications on newer fecal tests are deficient in this regard. PLMs are the ideal investigators, not only to participate in and facilitate the important research and development required, but also to ensure that study descriptions and data presentations fulfill the stated requirements.

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