Commentary

Improved colorectal cancer screening: a new option and opportunity

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Abstract: An important new test for colorectal cancer screening was evaluated by Imperiale *et al*. and reported in the April 4, 2014 *New England Journal of Medicine* entitled "Multitarget stool DNA testing for colorectal-cancer screening". This editorial notes the favorable trend in the reduction of colorectal cancer incidence and mortality, and explores the significant issue of suboptimal patient uptake of existing colorectal cancer screening examinations. The findings of the multitarget stool DNA test study are summarized, put into perspective, and the potential interest in this examination is considered. By expanding colorectal cancer screening uptake, the multitarget stool DNA test may further reduce the burden of colorectal cancer.

Keywords: Colon cancer; rectal cancer; colorectal cancer; colorectal neoplasia; cancer screening; cancer screening; stool DNA; multi-target stool DNA test; cancer testing; colonoscopy; fecal immunochemical test (FIT); stool occult blood; KRAS; NDRG4; BMP3; colon polyp; rectal polyp; colon adenoma; sessile serrated adenoma

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The distinctly encouraging journey toward prevention and early detection of colorectal neoplasia took another major step forward with the publication by Imperiale and colleagues of Multitarget Stool DNA Testing for Colorectal-Cancer Screening (1). The good news is that substantial progress is being made in the multi-faceted struggle with colorectal cancer. The annual update of data from the American Cancer Society published in January 2014 indicates that the incidence of colorectal cancer has been declining steadily between 2006 and 2010 by about 3.3% for men and 3.0% for women (2). Similarly, colorectal cancer mortality rates have decreased by 2.5% and 3.9%, respectively, over the same time period, and are down by 46% from their maximum (2). Long term reduction in incidence is thought to be due to reduction of risk factors and introduction of screening programs. The precipitous decline in incidence from 2008-2010, 4% per year, is thought to be due to the utilization of colonoscopy that has the ability to remove precancerous polyps (2).

Worldwide, at least 25 countries have implemented programs to screen for colorectal cancer (3). Most of these extensively use stool testing for occult blood or fecal immunochemical testing, but the United States, Germany, and Poland place a major emphasis on structural screening examinations of the colon (3,4). Several organizations in the United States publish colorectal cancer screening guidelines that are supported by virtually all healthcare insurance programs. In general, the guidelines suggest beginning of screening for average risk individuals at age 50, and include the options of colonoscopy every 10 years, flexible sigmoidoscopy every 5 years, or fecal immunochemical test (FIT) every year (5,6).

A significant problem with the current US screening recommendations is that the uptake by the population offered them is suboptimal. Quite simply, many patients who should be screened for colorectal cancer do not participate in screening programs. In the United States, the Center for Disease Control (CDC) conducts a regular national telephone survey of a representative sample of the population known as the Behavioral Risk Factor Surveillance System (BRFSS), and posts robust information about the health of the US population on its website (7). The latest results [2012] show that nationally, of those surveyed over age 50, 66.8% report having ever undergone a flexible sigmoidoscopy or colonoscopy. The greatest uptake was in Massachusetts at 76.7% and the lowest in

Alaska at 60.6%. Comparison to reports of mammogram uptake in women age 50 and above within the last two years over the very same period may shed light on an achievable public health opportunity. The Behavioral Risk Factor Surveillance System reports that nationwide, in women 50 and above, 77% have undergone mammograms in the last 2 years. The greatest uptake of breast cancer screening was in Massachusetts at 87.1%, and the lowest was in Wyoming at 64.5% (8). Although the CDC BRFSS data examines different diseases with different health optimization behaviors, an opportunity for increased colorectal screening examination uptake may exist if factors surrounding this screening, including characteristics of the examinations themselves, were enhanced.

Similar issues in colorectal neoplasia screening test uptake have been shown in other populations. When a cohort of 53,309 asymptomatic individuals aged 50-69 in Spain were offered colonoscopy or biennial FIT by a pre invitation letter, invitation letter, and two follow up letters, only 24.6% opted for colonoscopy while 34.3% selected the FIT screening program, (P<0.001) (9). Although cultural and social factors make comparisons of health optimization behaviors among different populations across the globe difficult, opportunities for improvement in colorectal cancer screening uptake may exist. The importance of the screening uptake issue is highlighted by The United States National Colorectal Cancer Roundtable. This organization, consisting of The CDC, American Cancer Society and other like-minded groups, is sponsoring a major initiative to get colorectal cancer screening rates up to 80% by 2018 (10).

When the population uptake gap of structural colorectal screening studies and the suboptimal performance characteristics of existing stool based screening strategies are considered, significant interest in development of an accurate noninvasive colorectal screening test emerged. Imperiale and colleagues used a novel multitarget stool DNA test and compared this to a commercial fecal immunochemical test (1). The new test quantitates mutant KRAS, aberrantly methylated BMP3 and NDRG4 promoter regions, controls for human DNA with beta-actin, also includes a built in immunochemical assay for human hemoglobin, and utilizes a logistic regression algorithm to provide a result. The authors studied a cohort of 9,989 asymptomatic average risk participants at 90 sites (private practice and academic) across North America having a screening colonoscopy. Of the cohort, 65 subjects (0.7%) were found to have colorectal cancer, and 757 (7.6%) had advanced lesions (adenomas or sessile serrated polyps >1 cm) on colonoscopy. The key finding was that the sensitivity of detecting colorectal cancer was 92.3% with the multitarget stool DNA testing and only 73.8% with FIT (P=0.002). Notable findings included the sensitivity of detecting advanced precancerous lesions at 42.4% with DNA testing and just 23.8% with FIT (P<0.001). The rate of detection polyps with high grade dysplasia was 69.2% with DNA testing and only 46.2% with FIT (P=0.004). The detection rate of sessile serrated polyps measuring 1cm or more was 42.4% for the DNA testing versus just 5.1% for the FIT (P<0.001). FIT had a higher specificity rate and had less subject samples rejected for technical reasons. The specificity with DNA testing and FIT were 86.6% and 94.9% (P<0.001), respectively, when subjects had no advanced or negative findings on colonoscopy, and 89.8% and 96.4% (P<0.001), among those with negative results on colonoscopy. The authors conclude that the multitarget stool DNA test detected significantly more cancers than FIT but had more false positive results.

It is clear that the multitarget stool DNA test significantly outperforms FIT on all the sensitivity based metrics evaluated: colorectal cancer detection, detection of advanced precancerous lesions, detection of polyps with high grade dysplasia, and detection of sessile serrated adenomas. As a cautionary note, the multitarget DNA stool test had lower specificity than the FIT test. The specificity of the multi-target stool DNA test correlated inversely with age. Potential reasons for declining specificity with age include lesions not detected by the index colonoscopy procedure or age related change in DNA methylation (11). Technical analytic problems resulting in subject exclusion were encountered more frequently in the DNA group than in the FIT group, both from insufficient material for analysis (213 *vs.* 34, respectively) and logistic issues with specimen shipping.

A large unanswered question is how the multitarget stool DNA test will be used in clinical practice. As the many currently unknown factors become clarified, the clinical role will be defined. On March 27, 2014 the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Panel to the US Food and Drug Administration (FDA) unanimously recommended (10-0) the test for approval (12). It is quite likely the FDA will ultimately approve a more sensitive noninvasive way to screen for colorectal neoplasia than is currently available. Unknown is what the manufacturer will charge for the test in each nation that it is offered. Also unknown is what comprehensive analytic modeling studies of projected use-alone, coupled with other tests, performed at varying intervals, including sensitivity analyses of charges for each test-might show.

Guideline promulgating groups have yet to make a clinical recommendation for use of the new test, an important point as many published clinical guidelines ultimately become health insurance payment policy. In spite of the large amount of uncertainty that exists now, it seems quite likely that many patients who currently will not accept a structural screening test of the colorectum may want this exam. Patients who are at above average procedural risk for a structural exam of the colorectum are also likely to be keenly interested in this exam. Furthermore, patients looking for the most sensitive way to screen their colorectum with a nonstructural exam are likely to be asking about this test. Even without the eventual modeling studies and forthcoming guidelines, the most important stakeholder in the colorectal cancer screening decision matrix is the patient, and the current suboptimal screening uptake suggests that an improved examination option may be welcomed.

Since the initial experience in 1969, and the reports by Wolf and Shinya of successful colonoscopic polypectomy in 1973, it has been widely recognized that colorectal cancer may be prevented by removing premalignant polyps (13,14). Until better dietary advice, more research supported physical activity regimens, and effective chemoprevention strategies emerge, the main way colorectal cancer will be prevented is by colonoscopic polypectomy. Although several colorectal lesion detection strategies exist, patient adoption has been suboptimal. By development of a more accurate examination that may enable additional patients to be willing to undergo colorectal cancer screening, the multitarget stool DNA test described by Imperiale is an important step in the journey toward reduction of the burden of colorectal neoplasia. Technological refinements and advancements in colorectal cancer screening will undoubtedly continue beyond this particular significant contribution (15). Once available, this new test offers the opportunity to expand colorectal cancer screening uptake and further reduce the burden of colorectal cancer.

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