EDITORIAL

Stool DNA and Colorectal-Cancer Screening

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Colorectal-cancer screening in the United States is a success story. The American Cancer Society recently reported that rates of death from colorectal cancer are down by 46% from their peak.[1] There is good evidence that screening efforts have played an important role in the trend.[2] However, work remains to be done, since approximately one third of Americans report not being current with screening.[3] One approach to increase screening uptake is to broaden the available test options. On the basis of current U.S. Preventive Services Task Force guidelines, there are three recommended options: fecal occult blood testing, flexible sigmoidoscopy, and colonoscopy.[4] Other screening tests, such as computed tomographic colonography and stool DNA testing, were not recommended because of insufficient evidence to assess the benefits and harms.

The evolution of stool DNA testing is also a success story. The test itself is inherently attractive, since it leverages knowledge of the biologic pathways leading to colorectal cancer.[5] However, early attempts to identify genetic and epigenetic changes in stool were fraught with challenges. In the first large-scale evaluation of stool DNA screening, only half of the 31 invasive cancers and less than 20% of advanced adenomas were detected.[6] However, substantial work has been done to improve the technology, including altering the marker panel and the collection buffer. Furthermore, a test for human hemoglobin was added to the genetic panel, and an algorithm was developed to determine a positive test from the individual assays.

Imperiale et al.[7] now report in the *Journal* the results of a large study of this new, multitarget stool DNA test. Sensitivities for the detection of colorectal cancer (92.3%) and advanced adenoma (42.4%) were much improved from the previous report and were significantly higher than for the one-time use of a fecal immunochemical test (FIT) for hemoglobin (73.8% and 23.8%, respectively).

Although the sensitivity of the stool DNA test is markedly improved, some caveats are worthy of note. First, the number of participants who were excluded from the study because of problems with sample collection or assay application was far greater in the stool DNA group (689 participants, or 6.3% of the total number) than in the FIT group (34 participants, or 0.3%). Given that colorectal cancer was detected in nearly 1 of 154 participants on colonoscopy, it is possible that 4 cancers would have been missed simply because of the complexity of the test. Second, this study compared only the one-time sensitivity of these two tests. Given the lower specificity and greater expense of stool DNA testing as compared with FIT, it is unlikely that the test would be performed annually in the way that FIT testing is recommended.[4] Imperiale et al. found that the sensitivity of FIT was similar to that of stool DNA testing for stage III and stage IV cancer but was lower for earlier stages. It is unknown whether annual FIT screening would detect these cancers before progression. However, it is known that repeated application of FIT improves the detection of neoplasia,[8,9] so only a long-term prospective study comparing stool DNA testing at a clinically defined interval with annual FIT screening would yield sensitivities for the detection of neoplasia that would be directly comparable.

Third, an even more important issue may be related to the specificity of stool DNA testing. Roughly 10% of the cohort had a positive stool

DNA result and entirely negative results on colonoscopy. This false positive rate is an important consideration when determining the appropriate interval for screening. Decision models are needed to guide how frequently this test should be applied as a screening tool to be cost-effective.[10] There is also the issue of heightened concern when a patient is found to have a positive stool DNA test but a negative result on colonoscopy. It is possible that some clinicians will choose to perform either earlier repeat colonoscopy or embark on further extracolonic workup for cancer in such patients.[11]

Finally, Imperiale et al. evaluated stool DNA testing among participants who had complete data for all three screening tests. However, real-world effectiveness may be different, particularly given the higher technical failure rate with stool DNA testing. The importance of compliance to the effectiveness of screening was evidenced in the COLONPREV study, in which a single round of FIT screening was equal to colonoscopy for cancer detection, most likely due to higher adherence with FIT.[12] Survey data suggest that stool DNA screening may be preferred to other options and could improve screening rates overall, but this hypothesis remains to be assessed in practice.[13]

The new multitarget stool DNA test is clearly an improvement over its predecessors, and the results of this study will help to inform the current effort of the U.S. Preventive Services Task Force to reevaluate screening tests.[14] Comparative-effectiveness studies are now needed to clarify the role of stool DNA testing with respect to programmatic screening with other test options. Only through a better understanding of other key factors, such as the screening interval, adherence, cost, and diagnostic evaluation of positive results, can we determine the appropriate place for stool DNA testing on the screening menu.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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