In 2016, the US Preventive Services Task Force (USPSTF) issued a Grade A recommendation for colorectal cancer screening using a range of equally acceptable screening modalities, including endoscopic, radiographic, and stool-based studies.\textsuperscript{1} This was the first time that the USPSTF included the multitarget stool DNA (FIT [fecal immunochemical test]-DNA) test as an acceptable screening modality. Fisher et al\textsuperscript{2} used longitudinal commercial and Medicare administrative claims databases to show steadily increasing use of FIT-DNA tests among individuals aged 45 years and older from August 2016 through July 2019. During this period, use of colonoscopy and non–DNA-FIT testing remained stable while fecal occult blood testing (FOBT) decreased. The USPSTF had noted that FOBT was less sensitive than FIT, which likely dissuaded use.\textsuperscript{1} Exact Sciences, which manufactures a FIT-DNA test and provided support for this study, has pursued a direct-to-consumer marketing strategy that may account for the testing trend. This trend may contribute to improved screening rates for colorectal cancer, but this has yet to be documented and the data should be interpreted with caution.

The FIT-DNA test combines a proprietary FIT with a number of DNA markers for colorectal cancer. Cross-sectional data have shown that the FIT-DNA test had a higher sensitivity for both advanced adenomas and colorectal cancer than a Polymedco FIT test.\textsuperscript{3} The specificity was lower, which may result in the need for more diagnostic colonoscopies, increasing health care costs as well as risks for complications. Guidelines recommend annual FIT testing, whereas the recommended interval for FIT-DNA testing is every 1 to 3 years.\textsuperscript{1,4} Therefore, the cross-sectional data may not accurately estimate FIT’s performance characteristics—potentially underestimating sensitivity and overestimating specificity compared with FIT-DNA.

Screening has been shown to reduce colorectal cancer incidence and mortality, with supportive data from randomized trials of FOBT and flexible sigmoidoscopy and observational studies of colonoscopy.\textsuperscript{5} Guidelines have accepted the concept that results from screening trials of annual or biennial guaiac-based FOBT tests can be extrapolated to other stool-based tests, such as FIT. However, the FIT-DNA, which is detecting both blood in the stool (FIT component) and DNA markers, has a more cumbersome stool collection and analysis process. FIT-DNA stool samples must be mailed directly to the company because analyses are not performed in traditional pathology laboratories, making it more difficult to integrate results into electronic medical records. Exact Sciences has not reported whether abnormalities in the FIT component and/or the DNA markers are giving rise to the positive tests. Additionally, we are not aware of any longitudinal FIT-DNA data on adherence with either the 1- or 3-year screening intervals or on the yield of colorectal neoplasia. Consequently, extrapolating results from FOBT studies to FIT-DNA might not be so straightforward. The Multi-Society Task Force rated FIT-DNA as a second-tier colorectal cancer screening test, reserving its highest ratings for colonoscopy and FIT.\textsuperscript{4}

False-positive results arising from FIT-DNA are also problematic. Although colonoscopy is not a perfect criterion standard, which also affects interpretations of the diagnostic performance of FIT testing, the positive FIT-DNA results may also be arising from neoplasia elsewhere in the aerodigestive tract. Retrospective observational data from the manufacturer found a low incidence of aerodigestive cancers among participants during a median follow up of 5.3 years after a negative high-quality colonoscopy and authors concluded that further testing was not warranted.\textsuperscript{6} However, uncertainty about the extent of diagnostic testing to pursue false-positive results, particularly to allay patient concerns, represents an important evidence gap.
The FIT-DNA test costs about $600 for patients with private insurance and about $500 for Medicare patients. These costs are approximately 15-fold higher than for FIT tests. Using FIT-DNA testing in large, organized screening programs could burden health care systems with limited resources, such as Federally Qualified Health Centers. A modeling study, using a range of equal participation rates based on observational data, found that screening with FIT or colonoscopy was consistently more effective and less costly than FIT-DNA testing—even at the Centers for Medicare & Medicaid Services approved 3-year testing interval. To be cost-effective, the authors concluded that FIT-DNA would need to achieve substantially higher participation rates than seen with FIT or be reimbursed at a lower rate.

If offering FIT-DNA increases screening among those who do not prefer colonoscopy or FIT, then this strategy certainly may help reduce the burden from colorectal cancer. However, while “the best screening test is the one that gets done,” more robust outcome data on FIT-DNA testing would help bolster clinician confidence in this expensive screening modality.

ARTICLE INFORMATION
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Corresponding Author: Richard M. Hoffman, MD, MPH, Department of Internal Medicine, University of Iowa, 200 Hawkins Dr, SE618 GH, Iowa City, Iowa 52242 (richard-m-hoffman@uiowa.edu).
Author Affiliations: Department Internal Medicine, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City (Hoffman); Holden Comprehensive Cancer Center, University of Iowa, Iowa City (Hoffman, Levy); Department of Epidemiology, University of Iowa College of Public Health, Iowa City (Levy); Department of Family Medicine, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City (Levy); Department of Medicine, University of California, San Francisco, San Francisco (Allison).
Conflict of Interest Disclosures: Dr Allison reported pro bono consulting for Freenome, which is developing a blood test for colorectal neoplasia. No other disclosures were reported.

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