EDITORIAL

Colorectal cancer screening: 80% by 2018. Colonoscopists simply cannot do it alone

The National Colorectal Cancer Roundtable (NCCRT) initiative "80% by 2018" is a shared goal in which more than 300 healthcare organizations have committed to having 80% of adults aged 50 years and older regularly screened for colorectal cancer by 2018. A range of organizations have signed on to join this initiative, including hospitals, health systems, health insurers, specialty societies, advocacy groups, physician groups, and industry. Current colorectal cancer screening rates are estimated to be 65% by the Centers for Disease Control and Prevention,[1] so this represents a major leap in national screening rates. Reaching the 80% by 2018 target can be expected to reduce the incidence and mortality from colorectal cancer by over 20% and 33%, respectively, by 2030.[2]

Gastroenterologists have championed colorectal cancer screening for decades, based on our first-hand experience of diagnosing this deadly disease and our understanding of the value of polypectomy in preventing colorectal cancer. Taking colorectal cancer screening rates to a higher level will require an understanding of the ways in which people make healthcare decisions. This requires a multidisciplinary effort including primary care physicians, health insurers, hospitals and health systems, employers, and community organizations. It also will require options other than colonoscopy to reach the 80% target. Colonoscopists simply cannot do it alone.

An effective colorectal cancer screening test should be sensitive, specific, safe, and acceptable to patients. Colonoscopy is highly accurate, but it is invasive and in recent studies has been shown to be less acceptable to patients than noninvasive fecal screening. The Barcelona, Spain, COLONPREV study is a randomized controlled trial comparing colonoscopy once every 10 years to biennial screening with the fecal immunochemical test (FIT). In the first round of screening, participants randomized to the FIT were significantly more likely to adhere to screening than those randomized to colonoscopy (34.2% vs 24.6%).[3] The net result of higher participation with the FIT was that a similar number of cancers were detected in both arms of the study (although fewer adenomas were detected in the FIT arm). However, patients in the FIT arm will have 4 additional rounds of screening over the ensuing 10 years.

In the United States, fecal screening also has been found to be more popular with patients than colonoscopy screening. In the federally qualified health centers of San Francisco, Inadomi et al[4] used randomization to determine which screening test primary care providers would offer to their patients during 3-month blocks: colonoscopy, guaiac fecal occult blood tests (gFOBT), or a choice between the 2 tests. When colonoscopy alone was offered, significantly fewer patients complied with screening compared with those who were offered gFOBT or a choice between the gFOBT and colonoscopy (38% vs 69% vs 67%, respectively).[4]

> Reaching the NCCRT goal of "80% by 2018" will provide tremendous benefit to our patients through early detection of cancer and also through cancer prevention by polypectomy.

Gupta et al[5] used mailed outreach to invite uninsured patients in Texas to screen for colorectal cancer. Participants were randomized to colonoscopy, FIT, or usual care (opportunistic screening referral). Mailed outreach was more effective than usual care, but 40% of the FIT invitees participated, compared with 25% of those invited for colonoscopy.[5]

At Kaiser Permanente, Northern California, we mail out over 500,000 FIT kits every year, and >60% are returned. Our program of the FIT as a supplement to colonoscopy has led to screening rates above 83% over the last 3 years. We also are seeing an associated decrease in colorectal cancer incidence and a shift to an earlier stage at diagnosis.

A recent meta-analysis demonstrated that the FIT is between 70% and 80% sensitive for colorectal cancer, with 94% specificity.[6] Advances in molecular biology have offered the promise of better markers to detect colorectal cancer and its precursor lesions more accurately than does the FIT. A recent, large, industry-sponsored screening study was reported in which nearly 10,000 participants were screened with colonoscopy, the FIT, and the latest-generation, multiple-target stool DNA test, which includes

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a high-specificity FIT. The multiple-target test was more sensitive than the FIT for colon cancer (92.3% vs 73.8%) and advanced precancerous lesions (42.4% vs 23.8%).[7] However, the standard FIT was more specific than stool DNA (94.9% vs 86.6%). In addition to a substantially higher cost for the stool DNA test, the multiple-target stool DNA test is more complex for patients to collect. Over 6% of stool samples could not be evaluated because of leakage or technical failure. It is unclear whether this complexity would result in fewer patients completing screening compared with the FIT, which would have an adverse effect on overall screening rates.

Blood-based markers are the presumed holy grail of colorectal cancer screening. Easy to obtain from patients when they are coming in for other preventive screening blood tests (such as cholesterol or hemoglobin A_{1c}), these marker tests would remove the "ick" factor of having patients collect fecal samples to complete their colon screening. Methylated septin 9 is one of the first tests to be marketed for blood-based screening. In their cost-effectiveness analysis, Ladabaum et al[8] found that an annual FIT was more effective and less costly than the methylated septin 9 test. Because of low sensitivity for early stage cancers (approximately 50%) and low specificity (70%), substantially higher uptake of methylated septin 9 screening compared with FIT screening would be required to make septin 9 a cost-effective screening alternative.

In this issue of *Gastrointestinal Endoscopy*, Overholt et al[9] report on their experience with a new blood-based marker for colorectal cancer, CA 11-19.[9] This study used serum from 522 participants recruited from 36 endoscopy clinics in Texas (200 patients) and 1 clinic in Knoxville, Tennessee (322 patients). The study population included a mix of patients undergoing colonoscopy for screening, surveillance, or diagnostic purposes. The study was enriched with 72 participants from the Texas clinics and 59 from the Tennessee clinic, who were patients preparing to be treated for colorectal cancer. Sensitivity appeared high, because 97.7% of people with colorectal cancer had a positive test result for CA 11-19, and 40% of people with an adenomatous polyp had a positive test result. Specificity was 84.4%. In addition, when stratified by stage at diagnosis, there was no drop in sensitivity for early stage cancers.

Although these results are promising, the study design and the way the results are presented limit our ability to draw meaningful conclusions from this report. This study used a case-control design. The main threat to validity is the potential for bias in the way cases and controls were selected for participation in the study.[10] Confounding occurs when there are important differences (other than the presence or absence of colorectal cancer) between cases and controls that may make them more or less likely to have a positive test result. For example, if the cases were older, more likely to smoke, were male, or were more likely to be of a particular race or ethnicity than controls, it could explain why they were substantially more likely to have a positive CA 11-19 test result. In addition to measurable sources of bias, there are other potential biases that may be harder to measure, such as diet, exercise, medication use, or employment exposures that may explain why the CA 11-19 test result was more likely to be positive in cases than in controls. In this report, no comparison of demographic or other risk factor information was presented to allow comparison between cases and controls.

An effective way to address sources of bias is to use a nested case-control approach, in which participants are selected and samples are obtained before the case or control status is known (in this case, before the colonoscopy is performed).[10] This allows investigators to be more confident that cases and controls were drawn from the same population. In this study, the 131 colorectal cancer cases appear to have been drawn from an entirely different population than the remaining 391 controls (the controls came for a surveillance, diagnostic, or screening colonoscopy, and the cases were drawn from people planning to have treatment or surgery for colorectal cancer). We can expect to see lower sensitivity and possibly lower specificity if this test were used in a prospective manner on patients before colonoscopy. This approach is substantially more expensive because approximately 10,000 participants would be needed to have enough colorectal cancers to provide meaningful results.

In summary, reaching the NCCRT goal of "80% by 2018" will provide tremendous benefit to our patients through early detection of cancer and also through cancer prevention by polypectomy. However, colonoscopy alone will not get us there. The FIT remains the most well-studied and easiest-to-use noninvasive test for mass screening. Molecular tests, either the stool DNA or the newer blood-based markers, are promising, but more study is needed. Because of the case-control design of this report on CA 11-19, it is difficult to know how this test will perform as an adjunct to colonoscopy for colorectal cancer screening or will assist in the diagnosis of people with suspected colorectal cancer. Over the next several years, we can anticipate reports of other new markers, but it is important to be sure that studies of new markers be conducted in a way that will allow the drawing of valid conclusions.

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Theodore R. Levin, MD
Gastroenterology
Kaiser Permanente Diablo Service Area
Walnut Creek, California, USA

Abbreviations: FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; NCCRT, National Colorectal Cancer Roundtable.

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