ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

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Colonoscopy vs Stool-Based Testing for Colorectal Cancer Detection

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G&H What is the current status of colorectal cancer screening in the United States, and what screening tests are recommended?

JD Based on colorectal cancer (CRC) screening data from 2023, approximately 63.5% of Americans aged 45 to 75 years are up-to-date; however, among those aged 45 to 49 years, the rate is much lower at about 37.1%. The screening tests that are recommended by the US Preventive Services Task Force include colonoscopy and stool tests, such as a high-sensitivity guaiac fecal blood test, a fecal immunochemical test (FIT), and a multitarget stool DNA test. Other screening test options include flexible sigmoidoscopy, flexible sigmoidoscopy in combination with FIT, and computed tomography (CT) colonography. The US Multi-Society Task Force, which is made up of representatives of the three major societies, the American Society for Gastrointestinal Endoscopy, the American Gastroenterological Association, and the American College of Gastroenterology, recommends a tiered approach to screening. Tier 1 screening tests include colonoscopy every 10 years or annual FIT, and then for those people who decline colonoscopy and FIT, they have the Tier 2 tests, which include the multitarget stool DNA test every 3 years, CT colonography every 5 years, or flexible sigmoidoscopy every 5 to 10 years.

> Colonoscopy has the best sensitivity of any of the tests and is considered the gold standard.

G&H What are the main benefits and drawbacks of screening with colonoscopy?

JD Colonoscopy has the best sensitivity of any of the tests and is considered the gold standard. It also provides the opportunity to remove polyps at the same time as screening, thereby preventing progression to CRC in the future. The main drawback is that it is the most invasive test. In most cases in the United States, colonoscopy is routinely performed with sedation, although that is not true everywhere in the world. Use of sedation requires that the patient have a driver or chaperone, and both the patient and driver may need to take time off from work. Colonoscopy also requires a bowel preparation, which many people say is the worst part of the procedure. There is also a small, but not zero, risk of perforation, bleeding, and other complications. Thus, colonoscopy has the benefit of being the most sensitive test and opportunity for polyp removal to prevent cancer, but it comes with some trade-offs.

G&H How are the different stool-based CRC screening tests performed?

JD FIT is a rather simple home-based test that the patient receives from a clinic, laboratory, or by mail. The test kit typically includes a flushable piece of paper that floats on

top of the toilet water. After the patient has a bowel movement on top of that paper, they use the provided collection device (eg, a stick attached to the cap of a tube) to coat the tip of the stick with stool and then insert the stick back in the tube, which contains a preservative buffer. After recording their information, including the date of collection, the tube with a stool sample is placed in a plastic bag and mailed in a return envelope or brought back to the laboratory. The process is fairly straightforward. As I mentioned, it is recommended that FIT be done every year.

The stool DNA tests currently on the market, including Cologuard and Cologuard Plus (Exact Sciences), are a little more involved. The test, which is mailed in a box to the patient, contains 2 collection devices. One is a bucket held by a bracket that is placed under the toilet seat, and the other is the same type of tube that is used for the FIT. The patient basically has to do a similar process to what I described for FIT, except that after emptying their bladder, the patient collects a full bowel movement in the bucket. They then use a FIT collection device to scrape a small sample of stool onto the stick as described above. Once that is complete, the patient adds a liquid preservative to the bucket, screws the lid on, fills out the labels, puts both containers in a plastic bag and into the box, and mails the box back to the laboratory. The stool DNA test, although slightly more complicated than the FIT, comes with printed and online instructions and there is an online video that explains the process. The Cologuard test is recommended every 3 years, which may help to improve adherence with screening.

Both tests have some time sensitivity. The most commonly used FIT needs to be received in the laboratory within 15 days of collection and is typically returned via standard mail. Cologuard has to be received within 72 hours, and because of that, the kit is returned to the laboratory via UPS and instructions advise not performing the test before a weekend. If either test is abnormal, then colonoscopy is recommended.

G&H What are the main benefits and drawbacks of stool-based tests?

JD On the benefit side, they are noninvasive and very convenient because they can be done at home. The one-time screening test cost is lower, but the sensitivity of the stool-based tests is not as high as it is for colonoscopy. As I mentioned, colonoscopy is required if the stool test is abnormal, and there are false-positive results. Comparing one-time screening head-to-head, the stool DNA tests have higher sensitivity than FIT for cancer, but FIT is done every year, and Cologuard is done every 3 years. Over 3 rounds of screening with FIT, statistical models predict that the sensitivity is very comparable to that of the Cologuard test. Cologuard is also more sensitive for advanced adenomas, which are the more worrisome polyps, and more sensitive for sessile serrated lesions. FIT has high specificity, meaning fewer false positives. Of course, with annual screening, longitudinal adherence is a little more challenging than with only every 3 years.

G&H How effective are stool-based tests in detecting CRC compared with colonoscopy?

JD Looking at the one-time use of a test, the sensitivity for detection of cancer is approximately 75% for FIT and 94% to 95% for the stool DNA test. Assuming 100% adherence, which is unrealistic, simulation models would find that screening colonoscopy has the greatest reduction in cancer incidence and mortality, with FIT coming in second, and stool DNA tests close behind FIT in third place. A few randomized controlled trials have compared invitations to screening with FIT vs with colonoscopy. The first is the Spanish COLONPREV study, which evaluated approximately 57,000 participants over 10 years, and found that an invitation to screen with FIT was noninferior to an invitation to screen with colonoscopy, as cancer incidence and mortality were statistically similar between the two groups. The second study, SCREESCO, published interim results after almost 5 years of follow-up earlier this year. This Swedish study found that invitations to colonoscopy and FIT were both associated with an increase in early-stage cancer incidence compared with usual care controls, although this increase was only statistically significant for colonoscopy. There were fewer late-stage cancers in both intervention groups compared with controls; however, this was only significant for the FIT group. The final results are expected around 2030.

Adherence is a key result of these studies. In COLONPREV, of those offered FIT, 39.4% completed at least one test over 10 years, whereas 20.1% of those offered colonoscopy underwent the test. Many people who were offered colonoscopy did FIT instead, so the colonoscopy group overall had a rate of screening of 31.8% because they had screening with FIT. In the FIT arm, only a half of a percent of those offered FIT crossed over to have screening colonoscopy. In SCREESCO, FIT participation was 55.5%, and colonoscopy participation was 35.1%. This is far below the 100% in the simulation models. When considering which test has better sensitivity, if a test is 100% sensitive but only half the people are willing to do it, the effective sensitivity is only 50%.

G&H Are the results of the COLONPREV study a valid representation of the risk of CRC mortality among individuals undergoing colonoscopy vs FIT?

JD This is where it gets interesting. The primary results I just mentioned are based on the intention-to-treat analysis. The study also looked at the overall cancer incidence and mortality in the population in a per-protocol analysis, which considers whether a patient's willingness to have a FIT or colonoscopy would have an impact on their risk of cancer incidence or mortality. The per-protocol analysis of COLONPREV showed that colonoscopy is associated with an 83% reduction in mortality compared with FIT. This was significant and suggests that getting a colonoscopy will result in a dramatic reduction in cancer mortality compared with FIT. The problem is that there is selection bias when offering a colonoscopy to people in a study like COLONPREV in that the people who volunteer to have the screening test tend to be healthier than people who do not volunteer (ie, the healthy volunteer effect). We need to be aware of this bias because part of the reason they are not getting CRC is that they are, in general, healthier. Perhaps these people tend to not smoke, drink less alcohol, exercise more, and do other things that affect their risk of CRC. Thus, I think the 83% mortality reduction has to be taken with a grain of salt, so to speak.

> Compared with no screening, all the tests are cost-effective.

The as-screened analysis of all the COLONPREV participants looked at what kind of screening they ended up doing and death from all causes. If they were in the FIT arm but got a colonoscopy, they were included in the colonoscopy group for the as-screened analysis, and if they were in the FIT arm and did not get screened with either FIT or colonoscopy, they were in the unscreened group. In this analysis, the 3 curves separate very quickly within a couple of years, where the colonoscopy group has the fewest deaths from any cause, closely followed by the FIT group, and then far worse is the no screening group. This is a demonstration of the healthy volunteer effect (healthy people get a FIT, very healthy people get a colonoscopy, and the least healthy have neither) because we would not expect colonoscopy or FIT to reduce all-cause mortality within a year or two.

G&H How does stool-based CRC screening compare with colonoscopy on cost-effectiveness?

JD A study by Ladabaum and colleagues, which I participated in, looked at the cost-effectiveness of the different screening tests and concluded that colonoscopy and stool-based screening tests have a profound impact on reducing CRC incidence and mortality. Colonoscopy is very cost-effective and offers the greatest benefit. FIT is less expensive overall but not quite as effective. There is a slight trade-off of saving money, but fewer lives saved. The stool DNA tests are somewhat more expensive and not quite as effective as colonoscopy or FIT. However, there is a clear divide between all the screening methods and no screening, with no screening resulting in much lower mean quality-adjusted life-years per person. Compared with no screening, all the tests are cost-effective. Again, these results assume 100% adherence. As participation in screening declines, less effective screening tests that have greater adherence can outperform a more effective test with lower adherence.

G&H Could you describe other CRC screening methods in development?

JD There are a few key ones that have been receiving attention. One is ColoSense (Geneoscopy), a multitarget stool-based RNA test, which is approved by the US Food and Drug Administration (FDA) and only very recently received a coverage determination from the Centers for Medicare & Medicaid Services (CMS). In addition to including FIT and stool RNA biomarkers, this test incorporates patients' history of smoking; having clinical history on smoking is necessary to factor into the determination whether the test is positive or negative. It has 94% sensitivity for CRC and 46% sensitivity for advanced adenomas. Another new screening method is blood testing, which I discussed in a previous column in *Gastroenterology & Hepatology*. Two well-known blood tests are Shield (Guardant Health), which is FDA approved and covered by CMS, and the Freenome cell-free DNA test, which is currently under FDA review.

One of the big questions is what the impact of people choosing the blood tests instead of the other approved tests will be. Currently, the blood tests are not recommended by the US Preventive Services Task Force guidelines. If they were to endorse the blood test, that could have implications for driving behavior with the Healthcare Effectiveness Data and Information Set, which measures rates of screening for CRC. The National Comprehensive Cancer Network and the American Cancer Society have endorsed the blood tests. Importantly, both organizations recommend blood-based screening only for individuals who have declined to be screened with one of the other accepted strategies, like colonoscopy or stool-based testing. This means that blood-based tests should not be offered as a first-line option. Of course, from a patient perspective, these blood tests sound appealing because having a blood test avoids the

hassle of collecting a stool sample and could be done at the same time as other routine blood tests. However, they have a few major problems. One is that the blood test is not very good at detecting precancerous advanced polyps. The chance of finding an advanced adenoma on routine screening is approximately 12%. For comparison, the sensitivity for finding advanced adenomas is approximately 25% for FIT and 40% to 45% for Cologuard. Thus, the stool-based tests are much better at detecting these lesions. My concern is that if people do a blood test instead of colonoscopy or stool-based testing, they will get false reassurance, and this will lead to worse outcomes for them and for the population overall since we are missing out on the opportunity to detect and remove polyps before CRC develops. If future scientific advances allow for improved detection of biomarkers for advanced lesions in the blood, it would be a real game changer. But from a biologic perspective, it would seem to be easier to detect biomarkers in the stool.

G&H What are the priorities of research?

JD As a gastroenterologist and a fan of colonoscopy, I think colonoscopy is a great test overall, but there are downsides that could be addressed. Continued innovation is needed to make colonoscopy even better, both in terms of overall effectiveness as well as improved appeal to patients. Despite years of efforts at quality improvement, we know there remains considerable variation in the quality of colonoscopy between different endoscopists. We need to determine the best ways to reduce that variability, such as through the use of better technique, report cards, devices, or artificial intelligence (AI) to aid in the detection of polyps. We may be able to improve adherence by making colonoscopy less burdensome for patients, such as by improving the bowel preparation process or reducing the need for sedation. A really important question is why are so many people not getting screened at all. We need to identify the barriers to screening and ways to overcome them, for instance, how to manage patients who forget or need assistance.

I believe that we will see a lot of research in the area of AI to improve screening outcomes. We need to understand how best to use AI agents, such as to assist with patient navigation for initial screening and for follow-up colonoscopy, or to optimize bowel preparation regimens based upon assessments of stool output. There are many questions about how AI may impact the training of endoscopists and whether it will lead to deskilling.

Overall, there have been dramatic improvements in CRC outcomes largely attributable to screening, but more still needs to be done to optimize the process. I am confident that our field will continue to innovate to make screening more effective and more efficient, and especially easier for patients, with an end goal of improving screening participation and reducing CRC morbidity and mortality.

Disclosures

Dr Dominitz has received grant funding from the Department of Veterans Affairs for studies comparing the effectiveness of screening colonoscopy with annual FIT screening for reducing mortality from CRC. He is president of the American Society for Gastrointestinal Endoscopy.

Suggested Reading

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