Epi proColon fires up hopes of capturing screening dodgers

Anne Paxton

November 2016—When a Hollywood producer forecasts box office receipts, or a public health official contemplates action against a deadly but preventable cancer, there's one hypothetical that might make both shudder: What if you held a screening and nobody came?

Fortunately, in colorectal cancer screening, no such scenario exists. Each year tens of millions of people are screened preventively or diagnostically with a fecal immunochemical test or a colonoscopy—frequently with the government or health plans signing the reimbursement checks. Still, in the past decade, about 35 percent of those who are eligible for screening in the U.S. have remained unscreened.

With the Food and Drug Administration's approval last April of Epi proColon, the first plasma test to detect the colon cancer marker methylated SEPT9 DNA, hopes are high that the percentage of people who shirk CRC screening will begin to fall.

Dr. Heichman

"We know there are populations that are going to refuse a colonoscopy and refuse a stool-based fecal test. They're not comfortable sending bowel movements in the mail, they're not comfortable with preparation and everything you need for a colonoscopy, or they're afraid of the procedure," says Karen A. Heichman, PhD, vice president and director of the PharmaDx program at ARUP Laboratories. A minimally invasive liquid-biopsy approach might be the solution. "Epi proColon is the first blood-based test with the potential to reach those patients who were never going to get screened for colon cancer."

New U.S. Preventive Services Task Force screening guidelines, published June 21 in *JAMA* (2016;315[23]:2564–2575), give a Grade A recommendation to CRC screening of average-risk, asymptomatic adults between ages 50 and 74. "Though the guidelines do not recommend specific screening tests by name, but rather by methods," says Nicholas Potter, PhD, FACMG, a member of the advisory board of Epi proColon manufacturer Epigenomics, "they acknowledged that there was a significant number of screening options, some new, that could be utilized, and they did not state a preference. That's important because what many people believe, and this is supported in the peer-reviewed literature, is that more options can help drive increased compliance through what is called 'the best test is the one that gets done' approach."

As it had done with Exact Sciences' Cologuard, a stool-based FIT and fecal DNA test approved by the FDA in August 2014, the FDA has also required Epigenomics to design and complete a post-market "real-world" study of effectiveness over time, says Dr. Potter, executive vice president of clinical affairs at Molecular Pathology Laboratory Network, Maryville, Tenn. "It's very hard to frame the concept of cost and cost-effectiveness to the health care system for some of these tests in the absence of longitudinal data. You need it because, in any programmatic screening endeavor, if you lose patients within the screening interval—whether it's annual, biannual, or once every 10 years—you obviously lose the effectiveness of your gains in programmatic sensitivity from testing people multiple times."

ARUP Laboratories has been at the center of the new blood test's development. A group led by Dr. Heichman devised a laboratory-developed test for methylated SEPT9 DNA based on the original assay design that Epigenomics used. The LDT was on the market for several years, as was a similar one that Quest Diagnostics developed. "That LDT was really the basis for the assay that went to the FDA, so we've been involved with this for a long time," Dr. Heichman says. ARUP is transitioning from its LDT to Epi proColon now that the FDA has approved Epigenomics' assay.
SEPT9 works as a marker because septin 9 hypermethylation occurs in the vast majority of CRC adenoma and tumor tissues that have been tested.

Historically, CRC testing is based on the fecal immunochemical test, an assay that has distinct advantages. "The specimen can be collected at home, the test is inexpensive, and if people have a positive test, they are referred for colonoscopy," Dr. Heichman notes. But stool-based testing has failed to gain traction. "People don't relish the fecal test. There's definitely an unmet need to get more people screened."

When Epigenomics submitted its premarket approval application to the FDA in 2013, the clinical information supporting the application included a study, led by Dr. Potter, showing that Epi proColon had a 68 percent sensitivity and an 80 percent specificity for cancer detection using colonoscopy as the comparator (Potter NT, et al. Clin Chem. 2014;60[9]:1183–1191). A study comparing FIT with SEPT9 showed Epi proColon had 73 percent sensitivity at 82 percent specificity, demonstrating "non-inferiority" to FIT as a CRC test (Johnson DA, et al. *PLOS One.* 2014;9[6]:e98238).

Initially, the FDA response to the Epi proColon application was less than encouraging. "The 2014 vote of the Molecular and Clinical Genetics Advisory Committee was 9–0 on the safety issue with one abstention, 5–6 with regard to effectiveness, and 5–4 with one abstention as to whether the benefits outweighed the risk," Dr. Potter says.

The 5–6 effectiveness vote prompted the FDA to issue a "not approvable" letter and request that Epigenomics perform an additional study to determine how the test might perform in real-life situations with regard to adherence and uptake, he explains. After this study (known as ADMIT, or Adherence to Minimally Invasive Testing, publication forthcoming) was completed, the data were submitted to the FDA and reviewed, and Epi proColon won approval.

How Epi proColon compared with already existing screening methods, most notably FIT, was a key question in the FDA's review, says Dr. Potter, who was part of the team that presented the data to the FDA. "Their question was, with a 68 percent sensitivity for detection of cancer at an 80 percent specificity, basically what you're telling us is you have a molecular test which is no better than FIT for cancer detection, but with an inferior specificity."

"In essence they weren't really sure, in the absence of any true effectiveness data, whether compliance or adherence could be increased by offering a blood test, and whether this would provide a substantial long-term benefit." That was why the FDA required the ADMIT trial before the recent approval of Epi proColon, Dr. Potter says.

"A lower specificity for Epi proColon means the potential for more colonoscopy referrals, and that's always a concern," Dr. Potter says. "Colonoscopy is not without risk—statistically it has 0.68 percent risk for an adverse outcome—and the use of Epi proColon compared to other noninvasive screening options is expected to result in additional colonoscopies." But since the additional patients should be screened anyway, "the use of Epi proColon shouldn't increase the risk above the standard of care."

Dr. Potter

False-positives, Dr. Heichman adds, are part and parcel of colonoscopy. “When they take a biopsy during a colonoscopy, it is based on morphology—what the lesion looks like—and with hyperplastic polyps, for instance, which are something you’d biopsy and take out during a colonoscopy, only a small fraction of those would potentially be cancerous. People live with polyps all the time, and most of them don’t turn into a cancer. We don’t know a good way of determining which ones of those would become cancer, and even when we take them out, we don’t know.”

The “specific intended use” language required by the FDA for Epi proColon, as stated in the packet insert, refers to adults of either sex, 50 years or older, defined as “of average risk for colorectal cancer,” who have been offered and have a history of not completing CRC screening.

This language reflects a tiered approach to screening, Dr. Potter notes, “because it recognizes that while certain other tests have better performance, as well as the ability to detect precancerous lesions, which Epi proColon does not do, similar to all non-imaging tests, the option of offering a blood test may get the unscreened screened.”

Outside the U.S., there has been a substantial amount of research and practical experience with Epi proColon, including a CE-approved version of the test offered in Europe since 2012. “The test has also been available in South America for several years, and in late 2014 a version was approved by the Chinese FDA for screening,” Dr. Potter says. The Chinese agency named Epigenomics’ blood-based test a “most innovative medical product” for 2015.

Epigenomics, which has a joint commercialization agreement with Polymedco, the largest U.S. distributor of CRC screening tests, to conduct nationwide distribution, is now offering Epi proColon through LabCorp, which intends to train and mobilize more than 1,000 sales representatives. ARUP, too, has launched the Epi proColon test, which provides another avenue for U.S. patients, Dr. Heichman says.

Equally important, there is a prominent role for smaller CLIA high-complexity laboratories to offer the test. “The test itself is essentially a duplex real-time PCR assay that interrogates the methylation status of the septin 9 promoter utilizing DNA isolated from plasma,” Dr. Potter says. “We’ve worked with this platform extensively. It’s run on standard instrumentation using very well-established molecular methodologies. It has a very flexible workflow, several pause points and hard stops are available if needed, and you can report a result with a one- or two-day turnaround.”

These features make the test a “good fit” for labs that are considering offering it or are charged by their institutions with providing all contemporary options for CRC screening, Dr. Potter says. “Like any other test, it requires that the laboratory bring in instrumentation if they don’t already have it. But many labs do have the PCR instrumentation and attendant resources to run Epi proColon. They would have to verify test performance, as opposed to validating it, and then determine its potential market. Since it’s an entirely new molecular test that is not complementing an already existing blood-based CRC screening assay, no one is going to have an existing market for this test.”

Widespread use of Epi proColon could lead to higher overall costs for CRC screening. “Currently Epi proColon is coded using an existing CPT code, 81401, with reimbursement in the $140 range,” Dr. Potter says. However, Epigenomics has already petitioned the AMA and was granted a new tier one code (81327) earlier this year, and in July it presented a justification to the Centers for Medicare and Medicaid Services for an allowance of

about $160 per test, which if accepted would place the test on the CMS 2017 clinical laboratory fee schedule.

But the least expensive screening approach, Dr. Potter explains, still remains FIT, which reimburses at about $22. For additional perspective, Exact Sciences' Cologuard, the combined FIT and fecal DNA test, reimburses at $493 to $650, depending on the payer. Screening colonoscopies are $770 to $1,300, while diagnostic colonoscopies—ones in which a polyp is removed—range from $975 to $1,800. While the absolute number of screening FIT and/or Cologuard tests performed annually may change with the addition of the Epi proColon option, if Epi proColon draws more average-risk patients into screening, the number of colonoscopies is likely to rise.

The payoff might be worth it. According to Epigenomics' model of cost-effectiveness, incorporating Epi proColon into the treatment paradigm of a 1 million health plan member population to reach 80 percent screening compliance would result in 179 additional cancer diagnoses at an incremental cost of $1.17 per member per month.

Beth Liles, MD, first started doing research on CRC screening in the mid-2000s. Dr. Liles is an investigator with the Kaiser Permanente Center for Health Research in Portland, Ore., and a methodologist with the Kaiser Permanente National Guideline Program. She compared the adherence of patients to Epi proColon versus Polymedco's OC Auto FIT in the ADMIT trial funded by Epigenomics and ordered by the FDA as part of the Epi proColon application for approval. "The FDA was requiring a study of real-world effectiveness," she says. "So we looked specifically at patients who were hesitant when offered either FIT or colonoscopy within their respective health systems. There was a significantly higher uptake of the blood test in comparison to FIT amongst patients who were hesitant to screen."

Dr. Liles

The implications of this study for what is the best population in which to use the blood-based test are not clear and will be the subject of further research, she says. "At a place like Kaiser Permanente, where fecal testing is our primary offer—we mail them to outpatients automatically on their birthday—we have a very high screening rate. The positivity of FIT is four to five percent. But the question is, can the blood test be a good option for people who don't like handling their own feces yet would be willing to do a follow-up colonoscopy if the blood test result were positive?"

Kaiser is not using the new blood test, Dr. Liles notes. "We would need to evaluate the test again in a research setting to evaluate how many patients would do the test if they knew of the risk of false-positives and if they were willing to do the follow-up colonoscopy, which was not something that was tested in our study."

Other research findings have added to the complexities of understanding the performance of Epi proColon. "One widely cited study tested an old version of the blood test, which used duplicate PCR. The newest version of Epi proColon uses triplicate PCR, which turns up the sensitivity at the cost of specificity. Another study, apparently in compliance with FDA study design requirements, evaluated the current version of the test among a subset of a population screened with colonoscopy."

"It's a tricky thing," Dr. Liles says. "I think the scientific community seems to want a far more expensive, robust, longer-term study to demonstrate the blood test's performance characteristics, and they haven't gotten that yet, so it makes it difficult for them to accept the studies that are out there."

Kaiser is not a good site for that research because it has a much higher than average screening rate, she says. "All the patients are so well screened; the rate is well over 80 percent here, and in other Kaiser regions it's 85 percent

and sometimes closer to 90 percent with the tests we offer. Which means if you use patients from our system, you're hardly going to get any cancer patients; you would be designing a study without a patient population."

To protect patients, she says, there needs to be shared decision-making with clinicians. "You have to tell patients there's a pretty good chance of a positive result, and check whether they will be willing to do a follow-up colonoscopy if there is a positive result. Because if not, patients should not do the blood test. It's not an effective protocol in that case."

Medicare, Medicaid, and related services have covered colonoscopy as a screening test since 2000 and most states have adopted similar legislation, says David A. Johnson, MD, a professor of medicine and chief of gastroenterology at Eastern Virginia School of Medicine, Norfolk, and lead author of the 2014 PLOS One study comparing FIT and SEPT9.

A past president of the American College of Gastroenterology, Dr. Johnson has had extensive leadership roles in developing guidelines on colorectal cancer, and he conducted the first screening colonoscopy trial in the world in the mid-1980s. In fact, he helped write the first legislation in the country mandating insurance coverage of screening colonoscopies for average-risk individuals, which Virginia adopted in 1999 and Medicare adopted in 2000.

When coverage of screening colonoscopy was first formally mandated, "the initial enthusiasm was very good. But we've plateaued in our ability to get beyond 62 or 63 percent of people who are eligible, based on their age, into CRC screening," Dr. Johnson says. Pap screening for cervical cancer and mammography for breast cancer, by contrast, have levels of 80 percent compliance. To address the problem, the American Cancer Society has joined with public health organizations in endorsing a CRC screening model with the goal, also championed by the Centers for Disease Control and Prevention, of having 80 percent compliance by 2018.

Dr. Johnson stresses the importance of recognizing Epi proColon as a blood-based cancer detection test—not as a cancer prevention test. For the purpose of guidelines, tests for CRC are divided into prevention and detection, and colonoscopy is an example of the former. "It's the best test for recognizing and removing a precancerous lesion to decrease the chance of that patient getting colon cancer." Over the decades, colonoscopy has dramatically helped prevent colon cancer and reduced the rate of death from CRC.

Moving to tests like Epi proColon and stool-based testing for DNA or blood, "we are much more in the cancer detection range," Dr. Johnson says. "We hopefully catch something at an earlier stage where it may be surgically resectable and curable. But that's just the point: We're catching cancer, not preventing cancer."

Blood tests looking at cancer pathways have been under development for some time, he notes. "There are a number of cancer detection tests and formulations and strategies and this is just the first one that comes to the market." But he applauds the diagnostics industry's response to the need. "We are still dealing with 153,000 colon cancers a year, and the second most common cause of cancer death in men and women. It's a sizable number of people, despite the fact that we have colonoscopy."

Anything that gets someone screened is better than nothing, he adds. "But patients and physicians need to understand the limitations of doing a test for cancer detection. Patients may say, 'I just want to get the blood test,' but they need to understand that for cancer prevention, colonoscopy is still the gold standard."

If all screening were to start with a blood test and proceed to colonoscopy if indicated, Dr. Johnson says, "that would be a major move backward, because the tests are only so sensitive in detection and they do not rule out actual cancer. They would only detect 71 or 72 percent of cancers, and certainly would not detect precancerous polyps." The role of colonoscopy should be untouched. "Unquestionably, all positives must have a colonoscopy, so referrals for colonoscopy should go up on that basis." He would see that as a positive step.

The FDA had one proviso in its approval of Epi proColon: a post-market approval study of longitudinal performance that must be conducted by the manufacturer. Such a requirement is not unusual, Dr. Johnson says. "It's frequently done by the FDA and is not a negative. They are just appropriately asking what is the utilization rate." According to Epigenomics, international research is planned that will compare Epi proColon to FIT in matched patients in Germany, study opportunistic and general population screening in China, explore extension of indications to familial syndromes in the U.S., and study response monitoring in South America.

While there are no current data showing that a blood test will reduce CRC mortality, "there are solid data showing that population-based screening by either gFOBT or sigmoidoscopy can reduce colorectal cancer mortality, and data from the National Polyp Study, published in 1993 and 2012, demonstrated that the removal of polyps results in both a reduction in CRC incidence and mortality," Dr. Potter says. With regard to colonoscopy, there are three ongoing, robustly powered clinical trials designed to address incidence and mortality, but "determining the degree of impact will take time, as these studies have to be run longitudinally over many years." The first of the three colonoscopy trials is targeted to be completed in 2021. As such, the impact of Epi proColon on clinical outcomes will require similarly robust longitudinal studies, he adds.

A few questions have been raised about Epi proColon's efficacy and whether it can be incorporated readily into routine practice. In a "Viewpoint" in JAMA, accompanying the U.S. Preventive Services Task Force report, Ravi Parikh, MD, MPP, of Brigham and Women's Hospital, and Vinay Prasad, MD, MPH, of the Knight Cancer Institute at Oregon Health and Science University, note the test's lower performance (2016;315[23]2519–2520). They argue that "allowing blood-based screening tests for colon cancer to have a lower standard than that of other screening tests risks prioritizing convenience over patient safety and health care value." The authors raise questions about whether the blood test can be incorporated into routine clinical practice. Is it a disruptive innovation or simply disruptive? they ask rhetorically.

That particular critique has been raised in the past, Dr. Johnson says. But he thinks the health system is well equipped to improve screening. "Primary care providers—including internists, family practitioners, GPs, and any provider in a given service typically driven by primary care, plus ob/gyns for a large percentage of women—are scored on their compliance with certain parameters, and one of the parameters used is compliance with guidelines. Colorectal screening is a standard part of that. Non-compliance by providers would be considered substandard and would have negative effects."

Drawing a comparison among screening strategies is difficult, ARUP's Dr. Heichman says. It's true that certain types of precancerous lesions that are flat are difficult to detect by colonoscopy. But "I don't know whether those are the ones we detect by fecal testing or by blood-based testing." The original studies that demonstrated the value of screening were in populations that weren't treated, she notes. But that population may not be the most useful comparator. "It's hard to know what would have happened if we didn't detect a cancer, and it's hard to know whether the cancers you detect would have been ones that would end up killing a person."

The methylated SEPT9 DNA laboratory-developed test that ARUP Laboratories developed in about 2009 was based on circulating cell-free DNA technology, which has gotten a lot of attention in recent years because of the interest in using it to detect cancer mutations in blood plasma. "You really needed to have the ability to isolate circulating cell-free DNA which comes from the tumor and be able to test it," Dr. Heichman says.

From her perspective, Epi proColon doesn't have any downsides. "I've spoken with my colleagues at universities and gastroenterology departments and they are very encouraged by this kind of test as it has the potential to bring screening to those people who have rejected it in the past." She notes that Epi proColon is included in the U.S. Preventive Services Task Force recommendation statement as one of the many possible tests that could be used for CRC screening.

A new factor in the equation is a bipartisan initiative on Capitol Hill to push Medicare to make a coverage determination for Epi proColon. On Sept. 28, Rep. Donald Payne (D-NJ), co-chair of the Congressional Men's Health Caucus, introduced a bill (H.R. 6275) with co-sponsors Charles Dent (R-Pa.) and John Delaney (D-Md.) that would

require Medicare coverage for all FDA-approved blood-based screening tests. Rep. Payne argues that the test will "enable historically underserved communities to more fully participate in screening."

From his experience as a clinical laboratory practitioner in East Tennessee for 25 years, Dr. Potter is optimistic about Epi proColon. "I know the potential impact that a test like this could have in colon cancer hotspots located in Appalachia and the rural south. This test can be a very valuable resource, not only for practitioners trying their best to get patients screened but also for patients themselves."

The larger context is that the new screening options like Epi proColon can allow the health care system "to shift the medical economic burden from one that is heavily leveraged toward the cost of CRC treatment to one that focuses on screening and prevention," he points out. "That's a powerful motivator for all stakeholders."

Dr. Potter believes the test will contribute greatly to the National Colorectal Cancer Roundtable initiative to raise compliance to 80 percent by 2018. "This test provides a great opportunity for labs to participate in an initiative that has significant medical merit and to be part of the solution with regard to getting otherwise noncompliant average-risk Americans screened for CRC."
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