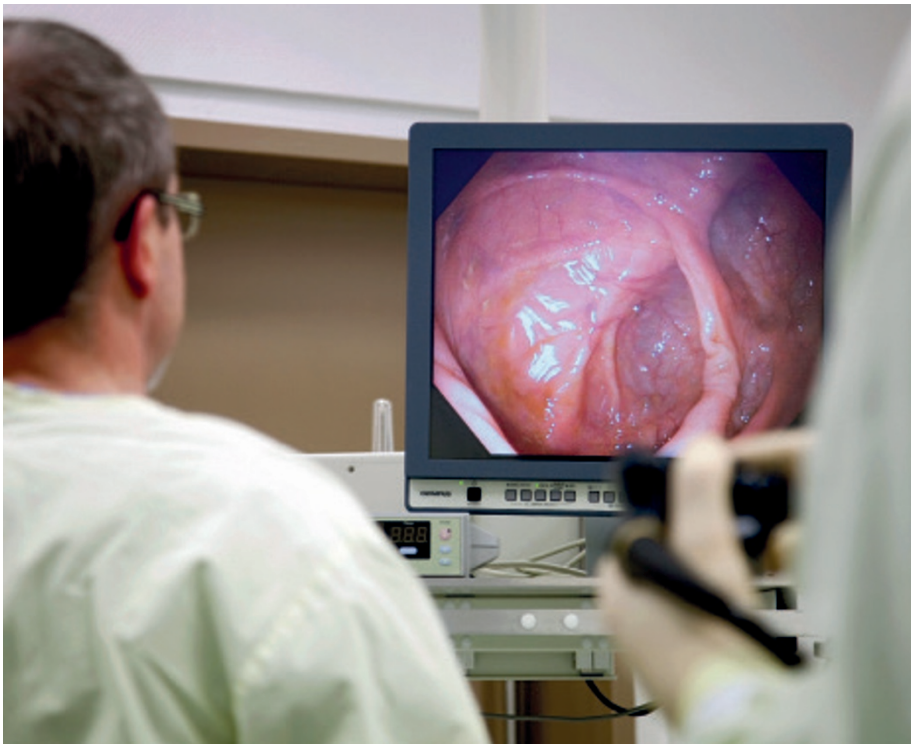


AGENCJA FOTOGRAFICZNA CARO/ALAMY

Colonoscopy is often the best method for identifying colon cancer at an early stage — but it is invasive.

SCREENING

Early alert

Scientists are developing an array of choices for screening colorectal cancer, but patients often choose to go without.

BY CASSANDRA WILLYARD

Every day, a UPS truck delivers dozens of identical white boxes to the back door of a nondescript building in Madison, Wisconsin. Inside each box is a miniature pail filled with human excrement. This faecal matter is bound for Exact Sciences' 3,000-square-metre laboratory, a sparklingly clean facility that analyses each sample for the genetic markers of colorectal cancer.

The test, called Cologuard, was approved by the US Food and Drug Administration (FDA) in mid-2014. It comes at a time when public-health officials in the United States are desperately trying to get more people screened.

Only about two-thirds of those eligible for colorectal-cancer screening in the United States have been tested. In March 2014, a coalition of organizations dedicated to reducing colorectal-cancer deaths announced a target of 80% by 2018. Exact Sciences provides its at-home test as an alternative for people who are not willing to have a colonoscopy, an invasive procedure that requires sedation and a clean bowel.

Although colonoscopy is by far the most common screening option in the United States, researchers have yet to demonstrate its effectiveness in a randomized controlled trial. Other countries have embraced cheaper, less-invasive tests that have proved to be effective.

"Our goal is to be able to have the most people screened with an effective test," says Douglas Corley, a gastroenterologist at the US health-care provider Kaiser Permanente in Oakland, California. This might mean combining existing tests to create more effective screening programmes, or looking for new strategies that are not only effective but also appealing enough for people to get tested.

KING COLONOSCOPY

In the 1980s, colonoscopies were rare. Instead, the American Cancer Society recommended either sigmoidoscopy, a less-invasive procedure that uses a shorter scope to view only the bottom portion of the colon, or the faecal occult blood test (FOBT), which identifies blood in the stool — a potential sign of cancer.

The FOBT uses a chemical called guaiac to detect the haem component of the oxygen-carrying protein haemoglobin. Early FOBTs were poor at detecting malignancy, but more recent high-sensitivity versions detect between 50% and 79% of colorectal cancers that are found with colonoscopy. A variant of FOBT called a faecal immunochemical test (FIT), which uses an antibody to detect globin in the stool, can pick up between 55% and 100% of cancers detected with colonoscopy. But stool tests do not involve peering inside the colon and so are less effective at detecting precancerous polyps — a major drawback because detecting and removing these growths can prevent colorectal cancer from occurring in the first place.

Oncologist Alfred Neugut of Columbia University Medical Center in New York was one of the first to suggest, back in 1988, that colonoscopy might offer better cancer detection. Neugut argued that the long colonoscopy tube would allow physicians to screen a larger portion of the colon than was possible with sigmoidoscopy, so it would detect more cancers.

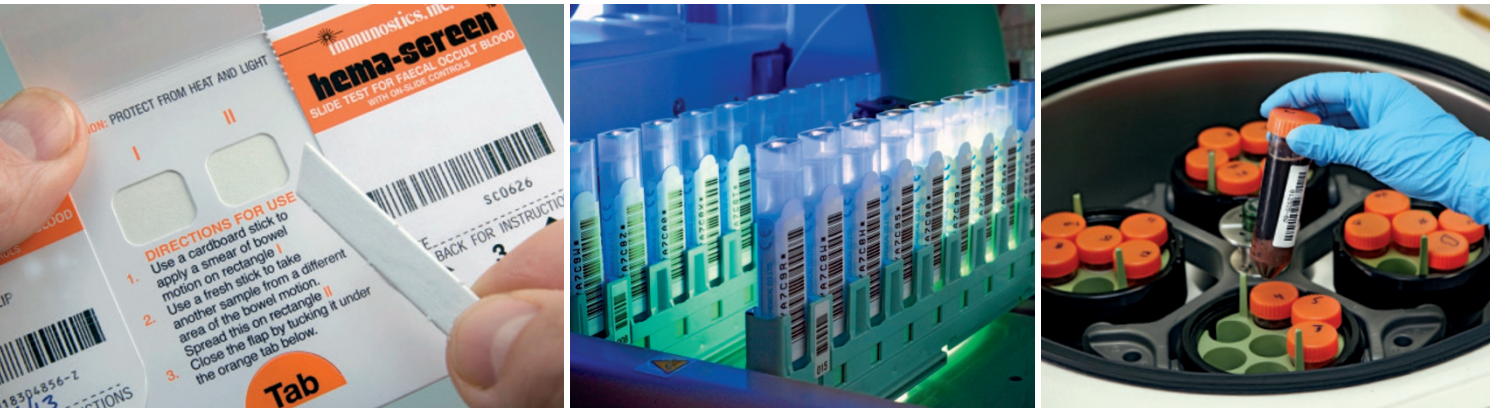
In 2000, US TV news personality Katie Couric, whose husband had died of colorectal cancer, encouraged her audience to have colonoscopies by undergoing the procedure on her show. In the same year, *The New England Journal of Medicine* published two studies[1,2] showing that colonoscopy can detect cancers missed by sigmoidoscopy. An editorial noted that "relying on flexible sigmoidoscopy is as clinically logical as performing mammography of one breast". The following year, federal health-insurance programme Medicare and many private insurers began paying for the procedure as a screening tool for colorectal cancer.

The US Preventive Services Task Force, an independent panel that issues evidence-based screening recommendations, lists three acceptable methods: FOBT alone, FOBT in combination with sigmoidoscopy, and colonoscopy. However, colonoscopy is the most common. According to 2012 data from the US Centers for Disease Control and Prevention, 65% of adults aged 50 to 75 reported being up to date with screening. The number screened by a colonoscopy within the past 10 years exceeded by more than 6-fold the number screened by FOBT in the past year, and by more than 60-fold the number screened with the FOBT–sigmoidoscopy combination.

If people could have only one screening test once in their lifetime, colonoscopy would be the clear winner, says Corley. But colorectal-cancer screening is not supposed to be a one-off event. The American Cancer Society recommends that people between the ages of 50 and 75 at average risk of the disease have either a colonoscopy every 10 years, a sigmoidoscopy every 5 years, or a stool test every year.

Colonoscopy brings a risk of bleeding and bowel perforation, and is less effective at catching cancer in the ascending part of the colon than in the descending portion.

NATURE.COM
For an animated overview of colorectal cancer, see *Nature Video*: go.nature.com/wgiqvp



The range of screening methods for colon cancer includes (left to right) stool blood test kits, faecal immunochemical tests and the Cologuard stool DNA test.

STEVE HORRELL/SPL; JAMES KING-HOLMES/SPL; EXACT SCIENCES

Three large, randomized trials have begun to study the value of colonoscopies, but they are unlikely to yield results for many years. By contrast, several trials have shown consistent results for FOBT and sigmoidoscopy. Sigmoidoscopy has been found to lower colorectal-cancer mortality by 22–31%, and FOBT reduces it by 15–33%.

Crucially, colonoscopies only work if people have them. In 2008, the US Preventive Services Task Force modelled the effectiveness of various testing strategies. With adherence at 80%, colonoscopy screening offered the greatest gain in life-years, followed closely by high-sensitivity FOBT and FIT. But when colonoscopy adherence was only 50%, it was no more effective than FIT, high-sensitivity FOBT, or either of those combined with sigmoidoscopy.

Other countries are keener to try the alternatives. In Australia, the National Bowel Cancer Screening Program sends FOBTs to people to use at home as they turn 50, 55, 60, 65, 70 and 74. Since the programme began in 2006, more than 4.6 million Australians have been offered the test, and 1.8 million have returned it for analysis. The goal is for all Australians between the ages of 50 and 74 to receive the test every two years by 2020.

The National Health Service (NHS) Bowel Cancer Screening Programme in England also favours FOBT. "It's recognized that colonoscopy is the gold standard," says Sally Benton, associate director of the NHS bowel-cancer screening hub in Guildford, UK. But the country lacks the resources to implement it.

In 2010, a team of UK researchers demonstrated the benefit of one-off sigmoidoscopy for colorectal-cancer screening[3], and the country is now running a pilot scheme for the procedure. Participants receive an invitation for sigmoidoscopy at the age of 55, and will receive FOBT kits every two years from the ages of 60 to 69.

DETECTING DNA

Cologuard provides another screening option. The stool test combines FIT with analysis to detect specific genetic markers — mutations in *KRAS*, a gene involved in cell division that is often mutated in colorectal cancer, and chemical modifications of two other genes associated with the disease. These markers provide a signature of the presence or absence of cancer, says David Ahlquist, a gastroenterologist at the Mayo Clinic in Rochester, Minnesota, who helped to develop Cologuard. "While many cancers and polyps don't bleed, they all shed cells."

Cologuard is not intended to replace colonoscopy — anyone who receives a positive result using any stool test still needs a colonoscopy to confirm it. But it does seem to have the edge over FIT. In a randomized trial[4] published in 2014, nearly 10,000 participants received either Cologuard or FIT in addition to a colonoscopy. Cologuard detected 92% of colorectal cancers compared with 74% for FIT, and found more precancerous lesions. But it also delivered more false positives: of those who had no evidence of cancer or advanced precancer when they received a colonoscopy, 13% tested positive using Cologuard. And the study did not examine how the test would compare to FIT in the long term.

Douglas Rex, a gastroenterologist at Indiana University School of Medicine in Indianapolis, points out that about 70% of Cologuard's performance is due to its FIT component. What's more, stool DNA tests are recommended once every three years, whereas FIT is offered annually. If FIT were performed annually for three years, as it should be, "you probably would make up some of that difference", he says.

Then there is the cost. In 2014, Medicare agreed to pay US$500 for a Cologuard test — much higher than its $5 reimbursement for FOBT and $22 for FIT. Even if a person took the FIT test annually, as recommended, it would still cost much less than Cologuard over three years. "It's a little bit tricky to know whether the extra cost is worth it," Rex says.

BLOOD TESTS

To overcome people's queasiness about providing stool samples, several companies are developing tests that require nothing more than a drop of blood. "Many people don't want to touch the stool," says Ann Zauber, a biostatistician at the Memorial Sloan Kettering Cancer Center in New York.

German company Epigenomics markets one such blood test in Europe, called Epi proColon, which looks for a particular chemical tag on a gene called *SEPT9*. A study involving 8,000 people published in summer 2014 found that Epi proColon detected 68% of colorectal-cancer cases[5], but it had a high false-positive rate of nearly 20%. And, Rex points out, the test has a lower sensitivity for early-stage cancers than for late-stage cancers, which have a lower survival rate. For these reasons, he says, "it's not a good test for colon-cancer screening". A 2013 cost-effectiveness modelling study suggested that screening with Epi proColon every two years would be less effective and more costly than the alternatives.

But Epigenomics is targeting people who are not now being screened. "We want to lower the barrier for these patients to enter the screening programme," says Thomas Taapken, chief executive of the Berlin-based company. "Our assumption is that a blood test would do that."

In June 2014, the FDA declined to approve the test and asked the company to produce evidence that Epi proColon will increase compliance. Six months later, Epigenomics launched a study in the United States to answer that question. Researchers will invite people who have been offered screening but failed to comply to come into the clinic, where they will be selected at random to receive either a take-home FIT test or an Epi proColon blood test.

In a perfect world, adults would be screened for colorectal cancer when they are supposed to be, with a screening method that is proven to be effective. But in the real world, compliance is rarely perfect. Ultimately, says Zauber, "the best test is the one that gets done". ■

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1. Lieberman, D. A. *et al. N. Engl. J. Med.* **343,** 162–168 (2000).
2. Imperiale, T. F. *et al. N. Engl. J. Med.* **343,** 169–174 (2000).
3. Atkin, W. S. *et al. Lancet* **375,** 1624–1633 (2010).
4. Imperiale, T. F. *et al. N. Engl. J. Med.* **370,** 1287–1297 (2014).
5. Potter, N. T. *et al. Clin. Chem.* http://dx.doi.org/10.1373/clinchem.2013.221044 (2014).