MedicalXpress

Study shows stool DNA testing for colorectal cancer has potential, but challenges remain

October 7 2008

The first generation of a stool DNA test to identify early colorectal cancer has limitations, according to a Mayo Clinic-led study published in the Oct. 7, 2008, issue of *Annals of Internal Medicine*. Results did not corroborate findings of an earlier multicenter study that showed stool DNA testing was more accurate than fecal blood testing for colorectal cancer detection. *

"But the concerns we identified with stool DNA testing are all solvable," says David Ahlquist, M.D., lead researcher in the study that included 4,482 participants and 22 academic medical centers. Researchers have hoped that stool DNA testing could be the user-friendly and accurate screening tool that would increase screening numbers.

More than half of adults in the United States have never been screened for colorectal cancer, the second-leading cause of cancer deaths. While available screening tools work, the most effective tests involve time, effort and costs. For example, colonoscopy requires fasting, bowel cleansing, a physician visit, sedation, an invasive procedure and lost work time -- factors that contribute to low screening participation.

This blinded study, conducted from 2001 to 2007, compared screening effectiveness of two widely used fecal blood tests (Hemoccult and HemoccultSensa) with a stool DNA test in average-risk patients, ages 50 to 80. The DNA test used was the prototype for PreGenPlus, the first commercially-used stool DNA test, and was performed on samples sent to EXACT Sciences in Marlborough, Mass. All participants underwent a

colonoscopy, the gold standard in current screening. Researchers used colonoscopy as the benchmark to detect cancer or precancerous polyps.

In the fecal blood screening, lab technicians searched for unseen traces of blood from stool that patients smeared onto a card. The presence of blood might indicate colorectal cancer. However, tumors bleed intermittently, which limits the test's accuracy for cancer detection. Three stool samples were tested for blood for each participant, the typical approach for fecal blood screening.

In DNA testing, researchers used sensitive laboratory tools to identify DNA from cells shed from cancer and precancerous polyps in stool samples. Only one sample was required because DNA shedding is believed to be continuous.

At about the study's halfway point, when 2,497 patients had been tested, researchers compiled an interim analysis. "All stool tests performed suboptimally," says Dr. Ahlquist. "The stool DNA test detected 20 percent of cancer and precancerous polyps, compared to 11 percent by Hemoccult and 20 percent by HemoccultSensa."

"We didn't think that stool DNA test performance was good enough to justify continuing without some changes," he says. Dr. Ahlquist and colleagues switched to a second-generation DNA test with improvements including a better method to capture DNA from stool and a more accurate panel of DNA markers.

With those changes, the stool DNA test performed significantly better than either of the fecal blood tests. "The new DNA test detected half of all the cancers and large polyps," says Dr. Ahlquist. In comparison, Hemoccult detected only one-sixth of cancers and large polyps, and HemoccultSensa found one-fourth of cancers and large polyps.

Importantly, the second-generation DNA test detected 46 percent of the precancerous polyps, compared to 10 percent detected by Hemoccult and 17 percent by HemoccultSensa. "If the premalignant polyps are not detected, cancer cannot be prevented. So, this result was most encouraging," says Dr. Ahlquist.

Dr. Ahlquist noted that the study, funded by the National Cancer Institute, honed in on weaknesses in the stool DNA screening that can be fixed to make it a more practical, accurate screening tool.

Sample degradation: Study participants were provided kits to collect and mail stool samples. When the samples arrived at Mayo Clinic's laboratory two to three days after collection, much of the DNA in samples had degraded and was not usable. "We have learned that adding a preservative at the time of collection eliminates DNA breakdown and can boost tumor detection rates further," says Dr. Ahlquist. That step will be important in future patient screening, should the test become widely available.

DNA markers: Markers used in the first-generation DNA test missed many polyps and cancers — evident in the low detection rate in the interim results. "The second-generation screen, with a broader assay, improved results," says Dr. Ahlquist. "We will be able to select even more accurate marker combinations for future tests."

DNA detection: Detecting the minute amounts of tumor DNA in stool is very challenging. Tumor DNA may account for less than one-millionth of total stool DNA. The instruments used to measure DNA for the interim results could not always detect the DNA. Since then, Mayo Clinic and others have improved the sensitivity of the measurement tools using digital polymerase chain reaction (PCR), a technique to duplicate DNA, and other analytical techniques.

"To prevent colorectal cancer deaths, we need an easy-to-use screening tool that consistently finds precancerous polyps," says Dr. Ahlquist. "Stool DNA testing is evolving quickly and may soon fill that need."

Earlier this year, the American Cancer Society endorsed stool DNA testing to detect colorectal cancer. Dr. Ahlquist advises that current hurdles to its use are that it is not widely available, has not been approved by the U.S. Food and Drug Administration, and is not covered by most insurers.

Source: Mayo Clinic