

OCTOBER 24, 2005

Blood Test Shows Promise in Early Identification of Colon Cancer

Researchers have developed a blood test that detects the presence of fragments of mutated genes that are present in colon cancer cells. Their pilot studies provide the basis for diagnostic assays for cancer that could allow physicians to detect tumors at an early stage.

The research team, led by Howard Hughes Medical Institute investigator Bert Vogelstein at The Sidney Kimmel Cancer Center at the Johns Hopkins Medical Institutions, published its findings on October 24, 2005, in the online Early Edition of the *Proceedings of the National Academy of Sciences (PNAS)*. Vogelstein and his colleagues at Hopkins collaborated on the studies with researchers from Israelitic Hospital in Germany.

"Assuming that future larger studies support these initial results, our hope is that such a test could be used to detect early tumors."

— Bert Vogelstein

"Each type of test for cancer has advantages and disadvantages," said Vogelstein. "One of the primary advantages of testing for mutations—compared with a test for PSA in the serum or blood in the feces, for example—is that mutations are not simply associated with the development of neoplasia. They are the causes of neoplasia." Indirect tests such as PSA or the fecal occult blood test can yield a positive result in the absence of cancer, he said, "so, at least in principle a much higher degree of specificity is possible when one is looking for mutations in genes that underlie a cancer."

The blood test is based on a technique called BEAMing, a name derived from the principal components used in the technique - metal beads, emulsion, amplification of DNA and magnetics. BEAMing involves attaching DNA fragments of a cancer gene from blood to metal beads and amplifying the number of copies of those fragments to a detectable level by using the polymerase chain reaction technique. The beads, with the DNA fragments tagged to denote whether they are normal or aberrant, can then be manipulated using magnetism and separated for measurement using a technique called flow cytometry.

The researchers tested BEAMing on blood samples drawn from colon cancer patients. They found that fragments of the cancer-causing gene, *adenomatous polyposis coli* (*APC*), were detectable in the blood samples. According to Vogelstein, the studies suggest that DNA fragments from tumors are released into the blood when immune system scavenger cells called macrophages destroy dead tumor cells.

Using a refined version of the BEAMing technique with improved sensitivity and specificity, the researchers tested whether they could reliably detect mutant forms of *APC* in blood drawn from 22 patients with colon cancer. They found they could easily identify mutant DNA in patients with advanced disease.

“When we analyzed the blood of patients with earlier stage cancers that were presumably curable by surgery, we could still find mutant DNA fragments,” said Vogelstein. “They were a smaller fraction of the DNA fragments compared with patients with more advanced cancers, but they were still detectable in more than sixty percent of the patients.” By contrast, blood from patients with benign colon tumors showed little evidence of mutant DNA fragments.

“While tests such as colonoscopy can detect more than eighty-five percent of colorectal tumors, including large premalignant ones, blood tests could prove useful for the large number of patients who don't undergo colonoscopy,” said Vogelstein. “Patient compliance should be very high, because most patients routinely have blood drawn when they visit their physician. And such tests should have high specificity because they detect mutations that are only present in cancer cells.”

While the test may one day be applied to diagnose a wider variety of cancers, those potential applications will depend on whether researchers can identify additional genetic mutations that are highly specific for each type of cancer, said Vogelstein. “In colon cancers, the mutations are well known, which sets the stage perfectly for this kind of test,” he said. “Similar tests should be possible for cancers of the stomach, ovary and pancreas. However, in other cancer types, such as those of the breast, only a relatively small number of mutations have been identified. So the broadness of this approach will to some extent depend on the discovery of more of the mutations responsible for other forms of tumorigenesis.”

The test could fill an important gap in the methods available for the early diagnosis of cancers. “For many cancers, such as those of the pancreas, stomach, lung and bladder, there really aren't any screening tests available,” said Vogelstein. “Assuming that future larger studies support these initial results, our hope is that such a test could be used to detect early tumors. And if the tests could detect even a third of patients with cancers who were pre-symptomatic and curable by surgery, that would represent an extremely useful advance.”