DNA-Based Colon Ca Screen 80% Sensitive

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PHILADELPHIA — A newly available, noninvasive screening test for colorectal cancer based on detecting a cancer-specific form of DNA had a sensitivity and specificity of greater than 80% in studies with a total of 363 people.

The indication for this screening test, known as ColoSure, is "people who refuse to have a colonoscopy," Dr. Sanford Markowitz said at a conference sponsored by the American Association for Cancer Research.

The test "has the potential to substantially lower the morbidity and mortality from colon cancer," said Dr. Markowitz, a professor of cancer genetics at Case Western Reserve University in Cleveland.

The new genetic test is "lousy compared with colonoscopy" as a screen for colon cancer, Dr. Markowitz noted, but many Americans older than age 50 years avoid colonoscopy screening despite the many guidelines that promote it. The new test is a better alternative than fecal occult blood testing (FOBT), he said.

Although a head-to-head comparison between the ColoSure test, which also involves testing a stool specimen, and FOBT has not yet been done, ColoSure was significantly more sensitive than a first-generation genetic-based stool test, PreGen-Plus; PreGen-Plus was previously shown to be significantly better than FOBT (N. Engl. J. Med. 2004;351:2704-14). This pair of findings is highly suggestive that when a head-to-head study is eventually done, ColoSure will prove to be more sensitive than FOBT, Dr. Markowitz said.

Marketing of the ColoSure test, made by Exact Sciences Corp., began in July. The test is offered by two companies: Laboratory Corp. of America (LabCorp), which requires a physician's prescription and charges about $240 as the retail price, and DNA Direct, which charges $399 for the test but will accept specimens directly from patients without a physician's involvement. The test is licensed by Case Western Reserve University, and Dr. Markowitz and his associates who developed the test receive royalty payments through Case Western.

Although Medicare coverage for the screen is still pending, colorectal cancer–screening guidelines published in May by the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology said that "there now are sufficient data to include sDNA [stool DNA] as an acceptable option for CRC [colorectal cancer] screening" (CA Cancer J. Clin. 2008;58:130-60).

The ColoSure test is based on finding a hypermethylated form of the gene that codes for vimentin, a filament protein that helps form cell structure. This hypermethylated form of the gene that's been found in roughly 80% of colorectal cancers probably has no direct relevance to the pathogenic process that results in colon cancer. "It's a marker that is probably downstream from cancer-causing changes," Dr. Markowitz said in an interview.

The screening test requires that patients send the testing laboratory a complete bowel movement with at least 36 g of stool. Immediately after the specimen is collected, it is treated and stored in a preservative solution that aids in maintaining the DNA content of the specimen. Once in the preservative solution, the specimen can be stored and shipped at room temperature.

Evidence for the efficacy of the stool test based on the vimentin gene was published online by Dr. Markowitz and his associates, who reported results from a two-phase study that involved 82 people aged 50 years or older who were known to have colorectal cancer based on a recent coloscopy examination, and 281 people who were free of colorectal cancer based on a recent screening colonoscopy. The sensitivity of the ColoSure test in combined results from both phases of the study was 83%, and the specificity was 82% (Am. J. Gastroenterol. 2008 Aug. 27 [doi:10.1111/j.1572-0241.2008.02088.x]). Sensitivity levels were similar regardless of tumor stage or location in the colon.

Dr. Markowitz and his associates noted that the false positives they found in the study may actually represent early detection of neoplasia before it becomes visible on colonoscopy. Although this notion will require confirmation, they suggested that if an apparently false-positive result from stool-DNA testing is encountered in clinical practice, the patient may need repeat screening by the stool-based test or by colonoscopy sooner than the generally recommended screening interval.

Work is also underway to find one or more additional DNA-based screening markers that could be added to the hypermethylated vimentin gene to boost the sensitivity closer to 100%. Dr. Markowitz said he was optimistic that additional markers will be found. ■

THE EFFECTIVE PHYSICIAN

Chronic Hepatitis B

BY WILLIAM E. GOLDEN, M.D., AND ROBERT H. HOPKINS, M.D.

Background

Chronic hepatitis B virus (HBV) infection remains a major public health risk. The Centers for Disease Control and Prevention has released recommendations to guide management of patients with this common viral illness.

Conclusions

The prevalence of chronic HBV infection in the United States is approximately 1 million patients, and the virus is responsible for up to 4,000 deaths a year. The majority of U.S. residents with chronic hepatitis B infections were born outside of the country.

HBV replicates in the liver after hematogenous dissemination. Immunosuppressed adults and children younger than 5 years are usually asymptomatic. Symptoms occur in only 30%-50% of patients over the age of 5 years. Symptoms of acute disease occur 2-3 months after exposure and include fatigue, anorexia, nausea, low-grade fever, abdominal pain, and jaundice. Duration of the illness is typically 2-4 months. The case fatality rate of acute hepatitis B is approximately 1%, with higher rates in the elderly.

Acutely infected patients who do not develop chronic hepatitis B will become hepatitis B surface antigen (HBsAg)–negative, hepatitis B core antibody (HBcAb)–positive, and HBsAb (anti-HBs)–positive.

Acute hepatitis B infection becomes chronic in more than 90% of infants, 25%-50% of children younger than 5 years, and less than 5% of the remaining population. Immunosuppressed patients and patients on hemodialysis have higher rates of conversion to chronic infection.

There are three phases of chronic HBV infection: immune tolerance (positive hepatitis B e antigen [HBeAg], high viral levels, inactive liver disease), chronic hepatitis (variable HBeAg status, high viral levels, and active liver disease), and inactive disease (positive hepatitis B e antibody [HBeAb], low viral levels, and normal transaminase levels). The presence of HBeAg and HBV DNA indicates high levels of viral replication. Anti-HBe usually reflects diminished viral replication.

Death from cirrhosis or liver cancer eventually occurs in 25% of chronically infected children younger than 5 years and 15% of older patients. Those with hepatic inflammation and fibrosis are at higher risk for hepatocellular carcinoma.

Patients with chronic HBV infection have a 0.5% rate of spontaneous resolution.

Implementation

The following populations should be tested for chronic HBV infection: those born in regions with prevalence greater than 2%, intravenous drug users, homosexual men, patients to receive immunosuppressive therapy, hemodialysis patients, all pregnant women, household contacts of patients with chronic infection, HIV-positive patients, and persons whose bodily fluids have been exposed to those of others, such as through needlesticks.

Detection of HBsAg is the primary method of diagnosis. No rapid or oral fluid diagnostic tests are available in the United States. All positive HBsAg laboratory results should be reported to local health departments in accordance with state regulations.

Most transmission of HBV results from close personal contact with patients who harbor chronic HBV infection. Among household contacts of chronic HBV patients, 3%-20% also harbor chronic HBV. A substantial minority of other contacts show evidence of resolved HBV infection. Chronic HBV infections are present in approximately 1% of homosexual men.

More than 90% of new infections worldwide have occurred in children younger than age 5 years by perinatal or household transmission. Hepatitis B vaccination has reduced incidence of the disease by 98% in children younger than age 15 years over the last 2 decades.

Sexual, household, and needle-sharing contacts should be identified and tested. Susceptible contacts should receive HBV vaccine. It is estimated that fewer than 20% of contacts receive vaccination.

Patients with chronic infection should be counseled about risks of transmission and techniques to reduce risks to contacts. They should cover skin lesions to prevent spread of infectious secretions, clean any blood spills with bleach, refrain from sharing household articles that could become contaminated with blood (such as toothbrushes or razors), employ safe sex techniques, and inform medical and dental personnel of their status prior to treatment. HBV is not spread by breastfeeding, kissing, coughing, or sharing eating utensils or glassware.

HBV remains infectious on environmental surfaces for at least 7 days. Nevertheless, no evidence supports transmission by workplace contact, and transmission rarely occurs in child care settings.

Chronically infected patients should receive hepatitis A vaccine in two doses 6-18 months apart if chronic liver disease is present.

There are seven FDA-approved therapies for chronic hepatitis B infection, and others are undergoing clinical trials. Optimal duration of therapy is not currently known. Combination therapy has not been shown to improve response rates, but more studies are needed.

Serologic end points of therapy include elimination of HBeAg, undetectable HBV DNA, and loss of HBsAg. Therapy should continue for at least 6 months after elimination of HBeAg and emergence of anti-HBe. Patients should be monitored for relapse after cessation of therapy.

Reference

Weinbaum CM, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR 2008;57(RR-8):1-20.

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