Can "DNA-based stool tests" replace colonoscopy in screening for colon cancer?

Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014; 370: 1287-97.

Original study is a cross sectional study, comparing a multitarget stool DNA test with a commercial fecal immunochemical Test (FIT) among patients at average risk for colorectal cancer and scheduled for screening colonoscopy.

Colon cancer takes place in the most common cancers of both sexes (1). The lifetime incidence of colorectal cancer for adults with an average risk is about 5%, and the disease proves fatal in about one third of those affected (2). Because of high detection rate of colonic lesions in curable stage, colon cancer screening has proven to be cost effective approach (3).

Currently, colonoscopy in screening for colon cancer is the most sensitive method. Colorectal cancer (CRC) screening is started in the average-risk individuals aged 50. Other methods to screen CRC include double contrast barium enema, fecal occult blood test +/- sigmoidoscopy and CT colonoscopy (virtual colonoscopy) (4). Considering all of these procedures, colonoscopy is the most effective method. Studies suggest that colonoscopy reduces deaths from colorectal cancer by about 60 to 70 percent. Expert groups recommend colonoscopy every 10 years for people at average risk as long as their test results are negative (5). In the case of sufficient bowel preparation, experienced endoscopist and enough withdrawal time, probability of detection of cancer and precancerous lesions is very high. Although colonoscopy is the most effective method, problems like patient unwillingness, lack of colonoscopy facilities, reimbursement issues, colonoscopy based screening programs are not successful as expected. Therefore, in CRC screening, non-invasive, highly sensitive and spesific, cheap and easily obtainable tests are still needed. The study of Thomas F. Imperiale and colleagues is a cross-sectional study. Participants with average colon cancer risk and scheduled to colonoscopy were included. Before bowel preparation, stool samples were collected for FIT and DNA tests, then following bowel cleansing, colonoscopy was performed.

Multitarget stool DNA test used in this study, consists of the following components: KRAS mutations, aberrant NDRG4 and BMP3 methylation, β-actin, plus a hemoglobin immunoassay. A total of 12 776 people from 90 centers participated in the study. Finally 9,989 people having all laboratory results and underwent colonoscopy were included. As a result, 65 colorectal cancer (prevalence 0.7%) and 757 advanced precancerous lesion (prevalence 7.6%) were detected endoscopically. The important point is that endoscopic prevalence of precancerous lesions is about ten folds more than CRC.

Multitarget stool DNA test was positive in 60 of 65 patients with colorectal cancer (sensitivity: 92.3% with 95% confidence interval). For precancerous lesions, sensitivitiy of multitarget stool DNA test was 42.4%. Regarding FIT, sensitivitiy rates were 73.8% and 23.8% in cancer and in precancerous lesions, respectively. DNA-based test to detect precancerous lesions are more successful than FIT. The sensitivity of a screening tests is the most important success criteria. The main purpose is to detect the precancerous lesions. As we understand from this study, DNA tests and the FIT have low success rates in detecting precancerous lesions (less than 50% of cancer detection rate). On the other hand, the FIT test is more specific (94.9 to 96.4% versus 89.8 to 86.6%). In summary, DNA tests are more sensitive, the FIT test is more specific.

Currently, the laboratory methods to screen colon cancer are not good enough to replace endoscopic screening methods. Despite progress in terms of being able to detect cancer, DNA-based testing is necessary to increase the sensitivity in precancerous lesions (6). The increase in sensitivity can be partially achieved with increasing variety of genetic markers, or modifying cut-

off values. With a better understanding of colon cancer pathophysiology, molecular biology and genetics, development of more sensitive and spesific laboratory tests may be possible.

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