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## COMMENTARY

### Colorectal Cancer Screening for Persons at Average Risk

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#### BACKGROUND

In the United States, colorectal carcinoma (CRC) is the fourth most frequently diagnosed and the second most common cause of cancer-specific death for both men and women (1). The life-time risk of developing CRC is approximately 6% (2), and treatment costs nearly \$6 billion annually (3). As for most epithelial cancers, CRC age-specific incidence increases continuously with biologic aging, with the greatest risk occurring in those individuals aged 80 years or older (2) (Fig. 1). Of the more than 148 000 estimated new CRC cases in the year 2002 (4), approximately 40% are expected to die within 5 years (2). Death from CRC is especially unfortunate, given that CRC prevention often can be achieved through screening (5).

CRC screening affords the opportunity to identify and remove precursor lesions (e.g., preinvasive adenomatous polyps or adenomas) (6). Indeed, direct, longitudinal observation of, and intervention in, the long-term, multi-step process of colorectal carcinogenesis—partially represented by the adenoma-to-carcinoma sequence in Fig. 2 (7,8)—can be achieved with existing endoscopic technologies (6,9,10). Although efficacy has been demonstrated in this regard, only 44% of U.S. adults aged 50 years or older have recently had any type of CRC screening (11).

To address these and other concerns, the National Cancer Institute (NCI) convened a workshop in March 2001 to review 1) routine and emerging CRC screening technologies, 2) valid endpoints (or targets) for CRC screening, particularly with regard to comparative evaluations of new and existing technologies; and 3) barriers to screening. This document with commentary from the authors summarizes the NCI workshop proceedings. Appendices A and D provide a complete listing of speakers and attendees.

#### ROUTINE AND EMERGING CRC SCREENING TECHNOLOGIES FOR PERSONS AT AVERAGE RISK

Approximately 75% of all CRCs occur among persons of "average risk," i.e., those without conditions such as inflammatory bowel disease, familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), or positive family history of colorectal neoplasia (adenoma or CRC) (12). While there is general consensus concerning the efficacy of CRC screening, slightly differing routine screening strategies are recommended by the American Cancer Society (ACS), the United States Preventive Services Task Force (USPSTF), and the American College of Gastroenterology (ACG) for average-risk individuals beginning at 50 years of age (5,13,14). In 2001, ACS recommended one of the following: annual home-based fecal occult blood test (FOBT), flexible sigmoidoscopy (FS) every 5 years, annual home-based FOBT plus FS every 5 years,

double contrast barium enema (DCBE) every 5 years, or colonoscopy every 10 years.

In 2000, the ACG recommended colonoscopy every 10 years as the preferred screening strategy for persons at average risk, whereas FS every 5 years plus annual FOBT was a reasonable alternative. DCBE every 5 years could be substituted for FS, if it is performed by a radiologist known to conduct high-quality examinations. In 1997, the USPSTF recommended FS (periodicity unspecified) or annual FOBT; new USPSTF recommendations are anticipated within the year.

#### Stool-Based Screening Tests

**Fecal occult blood test (FOBT).** The home-based FOBT is the most intensively and definitively studied routine CRC screening test. Nearly 350 000 individuals have participated in four FOBT randomized clinical trials—one in Minnesota (15–17) and three in Europe (18–20). Meta-analysis of these studies concluded that annual home-based FOBT reduced CRC incidence by approximately 20% and decreased CRC mortality by 16% (27). Acknowledged limitations of one-time FOBT include low sensitivity for adenomas (10%), low sensitivity for CRC (40%–85%), and relatively low specificity for adenomas and CRC combined (90%–98%) (28).

Sensitivity measures the probability of detecting either an adenoma or CRC, whereas specificity estimates the rate of false-positive tests (29). Although FOBT does not have direct toxic consequences, risk is associated with false-positive results, which may provoke unnecessary diagnostic endoscopic examinations with the potential to do harm. In contrast to one-time screening, the Minnesota trial estimated 90% sensitivity for a program of annual FOBT, i.e., programmatic FOBT (17,30). Additional improvements in stool-based tests could not only decrease the risk associated with screening but also decrease the number of people who need to be screened to reduce CRC incidence and mortality, which for FOBT is currently estimated to be 1400 persons to prevent one CRC death in 5 years (31).

**Fecal multi-targeted DNA-based assay panel (MTAP) test.** MTAP is a promising stool-based test that is currently in development (32,33). One example of MTAP targets 19 DNA

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