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# Advances in colonoscopy and screening for colon cancer

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A B S T R A C T

Physicians have a plethora of options when choosing a diagnostic test or procedure for colon cancer screening. Clinicians are no longer limited to fecal-occult blood tests and standard colonoscopy. Newer choices include advanced stool tests and imaging modalities like computed tomography colonography. Even the "standard" colonoscope has multiple accessories, ranging from simple plastic caps to multi-system high-definition imaging. Each new innovation brings with it data touting its excellence, and deciding the best modality can be a daunting task. As more information is learned about the natural history of precancerous polyps and colorectal cancer, screening guidelines have become more complex. This article reviews current screening modalities and new adjuncts to currently used techniques.



## Introduction

Screening for colorectal cancer (CRC) has been shown to decrease cancer-related mortality by approximately 33–60%.[1–3] There are multiple options regarding CRC screening including various stool tests, endoscopic platforms, and radiographic tests.

## Biochemical tests

### *Stool guaiac test*

Stool guaiac tests or fecal-occult blood tests (FOBT) were developed in the 1960s to detect the presence of blood in stool, presumably from a colorectal cancer. These would later become the commercial tests known as Hemoccult and Hemoccult II. The test is performed by applying a stool sample to a guaiac card and then adding hydrogen peroxide. A change in color (to blue) is considered a positive test. On the cellular level, luminal erythrocytes are lysed to free hemoglobin that is then converted to hematin and globin moieties. The peroxidase activity of hematin or hemoglobin is what catalyzes the oxidation of the colorless indicator compound to blue.[4] Early randomized controlled trials showed that these tests could reduce colorectal cancer mortality by 10–30% over 20 years of follow-up.[5,6] The incidence of CRC, however, was reduced only 20% in the same studies. Due to relatively low sensitivity and specificity, stool guaiac tests needed to be repeated multiple times to improve clinical reliability. Furthermore, in order to achieve accurate results, patients need to adhere to specific dietary restrictions prior to testing since iron contained in meats and catalases in certain vegetables could produce false-positive results. In addition, certain medications such as vitamin C could also interfere with chemical reaction on the sample card, thus producing false results. Thus, although FOBT could detect advanced adenomas and neoplasia, there was a definite need for improvement.

### *Fecal Immunohistochemical Test (FIT)*

The fecal immunohistochemical test (FIT) is an immunoassay designed to detect the globin moiety of hemoglobin. It can detect the presence and quantity of hemoglobin in stool. FIT testing is simple and requires only one sample to provide an accurate result. FIT testing is not limited by dietary sources of hemoglobin as the antibody is specific to human globin. It is also less likely to be affected by medicines such as NSAIDs or vitamins. As the test can be either quantitative or qualitative, different thresholds can be used to help detect polyps as well as CRC.[7] Fit testing is generally recognized as superior to FOBT, although to date there have been no randomized controlled trials directly comparing the two.[8] A recent meta-analysis of 19 studies examining the sensitivity and specificity of FIT found sensitivity to be 79%, specificity to be 94%, and overall accuracy to be 95%.[9]

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*Stool DNA*

The development of molecular tests in the early 1990s has allowed identification of genetic alterations in stool, which suggest malignancy. Compared to normal colonic epithelium, neoplastic and preneoplastic cells exhibit increased cell proliferation that leads to increased exfoliation of neoplastic cells and cell debris, which can be detected in stool. Initial stool DNA tests focused on targeting genes with chromosomal instability due to mutations in APC, KRAS, and p53. Another approach utilized targeting identification of DNA microsatellite instability (MSI) in stool samples. While the tests themselves were accurate, the overall sensitivity was poor, likely due to the overall low incidence of MSI in CRC.[10,11] The researchers did comment that MSI testing of stool could be useful in populations with hereditary non-polyposis colorectal cancer and also in combination with other assays.

The next DNA stool testing approached focused on identifying methylated genes in colon cancer cell lines.[12] Methylation alters gene expression by suppressing gene function usually during transcription. NDRG, TFPI2, vimentin, and BMP3 are all genes and gene families, which have been incorporated in screening tests for colorectal cancer. The NDRG (N-myc downstream regulated gene) family consists of four members, each having a tissue-specific expression. They encode cytoplasmic proteins required for the cell cycle. Melotte et al.[13,14] have extensively researched the NDRG gene family and have discovered that NDRG expression is decreased in cancer cells compared to normal cells. Methylation of the promoter region in colon cancer cell lines occurs in approximately 70–86% of cancerous tissues compared to $<5\%$ in non-cancerous tissues.[14] TFPI2 (tissue factor pathway inhibitor) is a serine protease inhibitor that has been identified as a tumor-suppressor gene. It functions by downstream inhibition of MMP (matrix metalloproteases), which in turn leads to decreased tumor invasion and metastases. Glockner et al. analyzed the colon cancer cell line HCT 116 (a commercially available colon cancer cell line) as well as samples of gastric, esophageal, pancreatic, and breast cancer. They found that TFPI2 was methylated in all the cell lines. On analysis of samples of known CRC (stage I–IV), methlyation was present in 99% of specimens. Considering cancer-free colonic tissues, methlyation was seen in only 6.2% of patients. Methylation was also observed consistently in polyps: 94% of serrated adenomas, 100% of tubular adenomas, and 100% of villous adenomas. Applying this approach using DNA extraction from stool samples, they found that detection of methylated TFPI2 had a sensitivity and specificity of 89% and 79%, respectively, for detecting stage I–III CRC.[15]

Vimentin is an intermediate filament protein that forms a major component of the cytoskeleton of mesenchymal cells. Its signaling pathway has previously been shown to be involved in the proliferation and migration of CRC cell lines.[16] Assessment of normal colonic tissues by polymerase chain reaction revealed methylation to be present in only 2% of samples. Samples of colon cancers, however, revealed methylation to be present in 46–83% of samples.[17] BMP3 (bone morphogenetic protein 3) is a growth factor with various functions throughout the body. Initially thought to only function in the formation of bone and cartilage, BMPs are also involved in the development of the cardiac and nervous systems. Multiple members of the BMP family have been shown to be involved in CRC, both with overexpression and downregulation. Specifically, BMP3 downregulation has been found to have an important role in the traditional and serrated adenoma pathways. Lo et al.[18] demonstrated downregulation in 89% of cancer cell lines, with definite hypermethylation present in 56%. About 76% of adenomas (serrated and traditional) exhibited methylation.

Currently, only one commercially available molecular assay is FDA-approved for CRC screening. The Cologuard stool DNA test from Exact Sciences was approved in August 2014. It consists of assays for aberrantly methylated BMP3 and NDRG4 genes, abnormal vimentin and TFPI2, abnormal KRAS, and an immunochemical assay for human hemoglobin. Imperiale et al.[19] evaluated 10,000 patients who underwent either Cologuard or FIT testing followed by colonoscopy within 90 days. About 67 patients (0.7%) had CRC and 757 patients (7.6%) had precancerous lesions (advanced adenoma or sessile serrated polyp $>1$ cm). The sensitivities for detecting CRC were 92.3% with Cologuard and 73.8% with FIT testing. The specificities were 86.6% and 94.9% for Cologuard and FIT, respectively. Cologuard was associated with a relative increase of 27% in the rate of detection of stage I–III colorectal cancers and 78% in the detection of advanced precancerous lesions. Both the tests had lower sensitivities for detecting precancerous polyps and polyps with high-grade dysplasia (approximately 30% for each test). Based on this, the number of patients needed to be screened to detect one cancer was 154 for colonoscopy, 166 with DNA testing, and 208 with FIT testing. While this does not change screening recommendations or the need for colonoscopy, it does add another non-invasive test to the arsenal of colorectal cancer screening.

## Colonoscopy

In terms of viewing the colon along its length, as well as sampling or removing any suspicious lesion, colonoscopy remains the gold standard. More than 14 million colonoscopies are performed every year. Screening for CRC using endoscopy reduces both the incidence of colorectal malignancies as well as mortality from those malignancies.[20,21] Using mailed questionnaires, Nishihara et al. analyzed data on 88,902 patients. They gathered information regarding personal history of polyps, CRC, and whether a patient underwent colonoscopy or sigmoidoscopy. Over a period of 22 years, there were 1815 documented CRCs and 474 deaths from CRC. When compared to the no-endoscopy group, colonoscopy and sigmoidoscopy were both associated with a reduced incidence of distal CRCs. Colonoscopy was also associated with a reduction in the incidence of proximal colon cancers. Endoscopic screening was also associated with reduced CRC mortality. They estimated that the incidence of CRCs that would have been prevented in patients who did not undergo follow-up colonoscopy was 40% overall (22% for proximal colon cancers and 61% for distal colon cancers). Negative colonoscopy was associated with a reduced incidence of proximal or distal colon cancers up to 15 years after the procedure, which supports current recommendations for 10-year intervals between scopes for average-risk patients with one negative colonoscopy. Finally, in patients who had an adenoma, overall cancer incidence was reduced for 5 years after colonoscopy. This benefit was less apparent in patients who had a high-risk adenoma.

Colonoscopy is usually an outpatient procedure, although it usually requires intravenous sedation. Patients are required to undergo a bowel-cleansing regimen. These regimens may be uncomfortable as they can lead to issues such as skin irritation, abdominal cramping, nausea, or dehydration. Complications of the procedure itself are infrequent but do include bleeding, pain, colon or rectal perforation, and failure to identify malignant or premalignant lesions. The perforation rate during colonoscopy is reported to be 0.03–0.7% and carries a mortality of 7–26%.[22] The polyp miss rate during colonoscopy is reported to be as high as 22%,[23] with smaller polyps being missed more frequently.

Technical problems, such as inability to completely visualize a polyp, are thought to be a major factor in missed lesions. Poor