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Colorectal Cancer Prevention Screening Tests; The Multi-Society Task Force Recommendations

Current colorectal cancer (CRC) screening methods are classified as invasive or non-invasive tests. The list of non-invasive tests is expansive and includes stool and blood-based tests and radiological tests. The stool-based available tests are guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), and newer fecal DNA test (Multitarget stool DNA, MT-sDNA, Cologuard). The newly emerging blood-based test is a qualitative polymerase chain reaction (PCR) test for the detection of mutated methylated septin9 DNA in plasma, detection of which has been associated with the occurrence of CRC. The radiological examinations include double contrast barium enema, capsule endoscopy, and computed tomography colonography (CTC). Invasive screening tests include colonoscopy and flexible sigmoidoscopy which offer direct visualization and detection of a colonic polyp or advanced adenoma with the advantage of getting a pathology specimen.

gFOBT detects presence of blood in fecal matter through a chemical reaction dependent upon the peroxidase activity of heme. The main advantages of the test are cost effectiveness, simplicity, and wide availability. The main disadvantage is interference due to presence of dietary peroxides, such as heme from myoglobin in red meat, peroxidase in plants, or anti-oxidants including vitamin C. The positive predictive value (PPV) of gFOBT is very low (3%-10%), due to non-specificity of the test. Regardless, a randomized study performed

in 1993 concluded that annual gFOBT with rehydration of the samples decreased the 13-year cumulative mortality from CRC by 33%.

FIT, considered a newer version of the guaiac based FOBT relies on the use of an antibody to human globin that does not cross react with dietary meats. In addition, FIT specifically detects colonic blood since the upper gastrointestinal globin is degraded readily by digestive proteolytic enzymes. The specimen collection is easy with fewer samples required compared to FOBT. FIT has greater sensitivity for detecting advanced adenomas and CRC than both standard and sensitive FOBT. A more recent systemic review and meta-analysis showed an overall accuracy of FIT for detection of CRC of 95% with a cumulative respective 79% sensitivity and 94% specificity. Disadvantages of FIT include low sensitivity for detecting colon polyps, variable accuracy between tests within a technology as well as between technologies, and cutoff levels.

Stool DNA Testing (Cologuard, the first multi-target stool DNA test approved by FDA for general CRC screening) targets molecular debris in stool including abnormal DNA present in malignancies such as KRA, actin, FIT, aberrantly methylated BMP3, and NDRG4 promoter regions. A multicenter comparative study reported fecal DNA test had higher sensitivity than FIT in detecting CRC (92% vs 74%). Unfortunately, the fecal DNA test performed poorly in detecting large advanced adenomas (42%), limiting its preventive role. Fecal DNA test has lower specificity at 87%-90% compared to FIT (95%-96%). A newer model-based

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study from Stanford University, showed that FIT and colonoscopy are more effective and cost-efficient than MT-sDNA, when participation rates were equal in all strategies (Ladabaum U and Mannalithara A. Gastroenterology 2016;151:427-439).

Methylated SEPT9 is based on detection of septins, a group of scaffolding proteins that provide structural support during cell division. FDA approved Epi proColon (also referred to as mSEPT9 assay), a qualitative Real-Time PCR test for detection of methylated SEPT9 gene in April 2016, as the first blood test for CRC screening. The initial prospective case-control studies, showed a higher sensitivity (70%) and specificity (90%) for CRC detection. A subsequent prospective trial in an asymptomatic screening cohort reported lower rate of sensitivity (48%), which further reduced to 35% in stage I CRC and to 11% in advanced adenomas practically eliminating its preventative role. Disadvantages include cost-effectiveness and potential for abuse leading to inadequate screening, and a need for second intervention, if the test is positive.

Typically screening tests should have high sensitivity and specificity, be safe, available, convenient, and cost effective. Since there are no published results of randomized trials directly comparing and reporting relative effectiveness of different tests on CRC incidence or mortality, the Multi-Society Task Force (MSTF) has grouped the available tests into 3 tiers based on the performance features and cost (Table 1).

Other factors that can influence CRC screening recommendations include age, race, and family history. A major public health concern in the recent years is the

reported increase in CRC incidence among persons under 50 years. Due to uncertain course of action to address this increase in the incidence rate, the initial step suggested is colonoscopy of patients with colorectal symptoms, especially with bleeding such as hematochezia, iron deficiency anemia, and/or melena with negative upper endoscopy. Patients with non-bleeding symptoms (e.g. abnormal bowel habit, change in bowel habit or shape, or abdominal pain) and no evidence of bleeding do not have an increased risk of CRC.

Two factors where earlier CRC screening is suggested include race and family history. Relative to other races, African Americans have higher incidence of CRC, younger age at onset, worse survival, and late-stage presentation, supporting an earlier screening age of 45 years. For individuals with high-risk family histories not associated with polyp syndrome, the onset age and interval for screening tests have been modified to every 5 years beginning at age 40 years or 10 years before the age the relative was diagnosed, whichever comes first.

Most of the screening tests in the United States result from an office visit to the healthcare provider, and are termed as opportunistic. Colonoscopy offered every 10 years, is the preferential screening test in such settings. In contrast, programmatic or organized screening is a system-wide, organized approach to offer screening to a population or members of a healthcare plan. Many large healthcare plans in the United States offer such screening, typically with an annual FIT testing. The burden of performing high-quality FIT testing falls largely on primary care physicians and

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should include the following MSTF recommended quality metrics –

1. FIT completion rate to those offered of 60% or more;
2. Proportion returning FIT that cannot be processed by the laboratory of < 5%;
3. Colonoscopy completion rate for those with a positive FIT of 80% or greater;
4. Adenoma detection rate >45% in men and 35% in women on colonoscopy examinations performed to evaluate a FIT-positive test that uses a hemoglobin threshold of 20 ug/g or less.

MSTF recommends offering screening tests as sequential (colonoscopy first, followed by FIT, if declined), multiple options (discuss and offer tier 1 options, followed by tier 2 and 3 tests, if declined), or risk-stratified (colonoscopy offered to patients with high pretest probability of neoplasm, and annual FIT test to patients with a lower pretest probability of neoplasm).

Table 1. Multi-Society Task Force (MSTF) ranking of current colorectal cancer screening test

Tier 1	Colonoscopy every 10 years
	Annual fecal immunochemical test (FIT)
Tier 2	CT colonoscopy every 5 years
	FIT-fecal DNA every 3 years
	Flexible sigmoidoscopy every 10 years (or every 5 years)
Tier 3	Capsule colonoscopy every 5 years
Tests Not Currently Recommended	Septin9

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