Colorectal Cancer: Valuable Screening Options

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The ideal screening technique for colorectal cancer

- Ability to detect disease at a curable stage
- Highly sensitive and specific
- Ability to elicit a high participation rate
- Affordable
- Safe for the patient and the physician
- More beneficial than the adverse effects
- Easy to perform

Introduction

- Colorectal cancer (CRC) is the second leading cause of cancer death and accounts for approximately 9% of cancer deaths overall
- Lifetime risk of CRC is 5% - 6% in Western countries
- Approximately one in three people who develop CRC die of this disease
- Approximately one-half of the cases of colorectal cancer diagnosed in the United States between 2004 and 2006 were late stage
- Screening rates for CRC is rising – 65.1% of adults between 50 and 75 years were up-to-date with CRC screening and 28% had never been screened

Adapted: Fletcher RH. 2014 www.uptodate.com
Introduction

• To reduce the incidence and mortality by screening, an interventional tool should:
  – Detect both advanced precursor lesions and curable-stage cancers from throughout the colo-rectum
  – Be patient-friendly, available and affordable

Predisposition to Colorectal Cancer

Family history
• Increase in lifetime risk related to family history of CRC ranges from about two-to-six-fold
• A family history of adenomatous polyps before age 60

Race
• Incidence and mortality from CRC are higher in African Americans compared with non-African Americans people
• CRC occurs at an earlier age
• Proximal lesions were more common in African Americans patients than non-African Americans patients
• Suggestion: Begin screening at age 45

Gender
• Prevalence of advanced adenoma (8.0 vs. 4.3%) and colorectal cancer (1.4 vs. 0.8%) are higher in men

Behavioral
• Smokers, compared with those who never smoked had an increased risk for CRC of approximately 20% (RR 1.18,95%)

High-risk genetic syndromes
• Hereditary nonpolyposis colon cancer (Lynch Syndrome) accounts for 2 to 3% of colorectal cancers
  – Increase risk for cancers other than colorectal, including endometrial, stomach, ovaries, pancreas, uterus and kidney, bile duct and brain (usually glioblastoma)

Adapted: Fletcher RH. 2014 www.uptodate.com
### Specific clinical risk factors for colorectal cancer

**Personal History**
- A prior history of CRC increases the risk of another primary (metachronous) cancer
- History of adenomatous colorectal polyps, especially if they are multiple, large or have villous architecture

**Abdominal radiation**
- Adult survivors of childhood malignancy who received abdominal radiation are at an increased risk of subsequent gastrointestinal neoplasms, the majority colorectal
- Approximately 11 times the incidence in people not exposed to childhood radiation and colorectal cancer occurred at a relative early age (<50 years old)

**Radiotherapy for prostate cancer**
- Associated with increased risk for rectal cancer; the hazard ratio

*Adapted: Fletcher RH. 2014 [www.uptodate.com](http://www.uptodate.com)*

### Specific clinical risk factors for colorectal cancer

**Endometrial cancer at a young age**
- Fourfold increase in risk of CRC for women diagnosed with endometrial cancer at age 50 years or younger (Lynch syndrome)

**HIV-infected male patients**
- Over age 50 may have a higher prevalence of colon neoplasms compared with the general population

**Inflammatory bowel disease – Ulcerative colitis and Crohn's colitis**

*Adapted: Fletcher RH. 2014 [www.uptodate.com](http://www.uptodate.com)*

### Detecting people with increased risk of CRC

**Guidelines to take into account - only personal history**
- Have you ever had colorectal cancer or an adenomatous polyp?
- Have you had inflammatory bowel disease, ulcerative colitis or Crohn's disease?
- Have you received abdominal radiation for childhood cancer?
- Do you have a family history of polyps and cancer
- Have any family members had colorectal cancer or an adenomatous polyp?
  - Were they first-degree relatives (parent, sibling or child)
  - Age at cancer or polyp diagnosis
- Are there any other cancers in your family?

*Adapted: Fletcher RH. 2014 [www.uptodate.com](http://www.uptodate.com)*
Colorectal cancer screening: ACP recommendations

Guidance Statement 1
- Age
- Race (African Americans have the highest incidence of colorectal cancer compared with other races)
- Family history
- Hereditary nonpolyposis
- Colorectal cancer in a first-degree relative, especially before age 50


Guidance Statement 2
- Clinicians should screen for colorectal cancer in average-risk adults starting at age 50 and in high-risk adults starting at age 40, or 10 years younger than the age at which the youngest affected relative was diagnosed with colorectal cancer

Guidance Statement 3
- Using a stool-based test
- Optical colonoscopy for average-risk patients
- Optical colonoscopy for high-risk patients
- Use colonoscopy as a follow-up for positive test results
- ACG recommends screening every 5 years for patients at high risk because of family history
- Computed tomography colonography is an option for screening in average-risk patients older than 50 years – not recommended by the US Preventive Services Task Force (USPSTF)

Guidance Statement 4
- Clinicians should stop screening for colorectal cancer in adults over age 75 or in adults with a life expectancy of less than 10 years


Preventive Services Task Force guidelines

- Fecal occult blood testing
- Flexible sigmoidoscopy
- Colonoscopy

Adapted: Robertson DJ, Dominitz JA. N Engl J Med 2014;370(14):1350-1351
Summary of the characteristics of screening tests for colorectal cancer

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Test performance (sensitivity, specificity)</th>
<th>Complexity</th>
<th>Potential effectiveness</th>
<th>Direct evidence of effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal occult blood test</td>
<td>Intermediate for cancers, low for polyps</td>
<td>Lowest</td>
<td>Lowest</td>
<td>Strong</td>
</tr>
<tr>
<td>Fecal immunochemical test for hemoglobin</td>
<td>Intermediate for cancers, low for polyps</td>
<td>Low</td>
<td>Low</td>
<td>Weak</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy</td>
<td>High for up to half of the colon</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Strong</td>
</tr>
<tr>
<td>FOBT + flexible sigmoidoscopy</td>
<td>Same as flexible sigmoidoscopy and FOBT</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Weak</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Highest</td>
<td>Highest</td>
<td>Highest</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Computed tomographic colonography</td>
<td>High (similar to colonoscopy)</td>
<td>High</td>
<td>High</td>
<td>Weak</td>
</tr>
</tbody>
</table>

The CRC screening guidelines for the United States in 2008

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Recommended Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>gFOBT</td>
<td>Annually</td>
</tr>
<tr>
<td>FIT</td>
<td>Annually</td>
</tr>
<tr>
<td>Stool DNA</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

Guaiac FOBT

- Detects peroxidase activity of heme and is not specific for human blood
- There is a better detection of cancer and large polyps with 2 or 3 stool samples obtained on separate days compared with one sample
- False-positive tests may occur if patients consume red meat or peroxidase-containing foods, and false-negative tests may occur when consuming vitamin C

Adapted: Fletcher RH. 2014 www.uptodate.com

Adapted: American College of Gastroenterology

Adapted: Lieberman D. Gastroenterology 2010;138:2115-2126
Guaiac FOBT

Cont.

• Little evidence that the predictive value is impacted by using non-steroidal anti-inflammatory drugs or anticoagulants

• Current guidelines do not recommend stopping these medications for testing

• Performed only once (with 3 stool samples), it is not very sensitive for neoplasia, detecting 13% - 50% of patients with cancer and 11% - 24% of patients with advanced adenomas (defined as tubular adenoma ≥ 10 mm, adenoma with villous histology, or high-grade dysplasia)

Adapted: Listerman G. Gastroenterology 2010;138:2115-2126

Guaiac-based fecal occult blood test (gFOBT)

• Lower mortality reductions (15% - 18%) reported in randomized trials of biennial screening with non-rehydrated specimens

• A program of repeated testing has a higher sensitivity of about 80% - 90%, compared to single test (40%)

• No need for a restrictive diet as decreased screening compliance, nor avoidance of stool iron supplements

• Doses >250 mg, q.d of vitamin C cause false-negative tests – avoid for 3 days prior to testing

• Do not rehydrate specimen

• A single stool specimen obtained during a rectal examination is not an adequate screen for colorectal cancer
  – Sensitivity for advanced neoplasia was 5% vs. a six-sample home test was 24%

Adapted: Fletcher RH. 2014 www.gribbins.com

Fecal Occult Blood (FOB):
Controversial areas

• Presence of FOB detected in the stool at the time of DRE should be managed in the same fashion as FOB detected in spontaneously passed stools

• Fecal blood content in therapeutically anticoagulated patients is within normal limits

• The combination of aspirin and warfarin leads to slightly increased levels of FOB, but neither warfarin nor low-dose aspirin alone seem to cause positive guaiac-based FOB tests

Adapted: Rockey DC. Nat Rev Gastroenterol. 2015;12:265-279
Fecal immunochemical test for CRC

- Antibodies specific to human hemoglobin, albumin or other blood components, is more specific for human blood and less prone to false-positive tests related to diet than gFOBT
- Detection rates for cancer exceeding 50%, using 1-3 stool samples
- Detection rates for advanced neoplasia are 25% - 30% in most studies using a qualitative FIT
- In quantitative test, the sensitivity for advanced neoplasia (including cancers) is as high as 67%

Adapted: Lieberman D. Gastroenterology 2010;138:2115-2126

Immunochromatographic tests for fecal blood

- Somewhat more sensitive and more specific than Hemoccult II for CRC and advanced neoplasia detection
- Sensitivity of the immunochemical FIBT declines with delay in mailing or processing after sampling because of hemoglobin degradation
- Quantitative immunochemical stool tests offer the ability to adjust the cutoff point for an abnormal result
  - 75 ng/mL provided a good compromise between detection rates of advanced neoplasia or colon cancer and the number of colonoscopies needed
  - No difference in the positive predictive value for advanced colorectal neoplasia of an abnormal FIT

Adapted: Fletcher RH. 2014 www.uptodate.com

Accuracy of fecal immunochemical tests for colorectal cancer

Meta-analysis of the diagnostic accuracy of FITs for CRC and identifying factors affecting its performance characteristics

- The pooled sensitivity was 0.79 (95% CI, 0.69 to 0.86), specificity (94%), positive likelihood ratio and negative likelihood ratio of FITs for CRC with an overall diagnostic accuracy of 95%
- Sensitivity for CRC improved with lower assay cutoff values for a positive test result (e.g. 0.89 [CI, 0.80 to 0.95] at a cutoff value less than 20 µg/g vs. 0.70, at cutoff values of 20 to 50 µg/g) but with corresponding decrease in specificity
- To optimize use of a quantitative FIT, consider the tradeoff between increasing sensitivity (by lowering the cutoff threshold for a positive test) and the resulting increase in the number of positive test results, which will have a greater effect on colonoscopy resources

Fecal DNA Tests

- A gene amplification technique allows detecting of lower abundance mutations with increased sensitivity for advanced adenomas
- False positives (not found to have colonic lesions on colonoscopy)
  - Etiology: uncertain — may indicate upper gastrointestinal neoplasms or premalignant genetic abnormalities
- Sensitivity from 62% to 100% for colorectal cancer and 27% to 82% for advanced adenoma
- Specificity from 82% to 100%

Adapted: Fletcher RH. 2014 www.uptodate.com

Advantages of stool genetic testing

- Improved sensitivity and specificity over FOBT
- Unlike bleeding that may be intermittent, colonocytes are continually being released, and therefore a single specimen is sufficient
- Small amount of specimen required


Colorectal Cancer Screening by fecal mutant DNA

Goal:
- To detect mutant DNA from shed tumor cells in fecal material for colon cancer screening to increase in diagnostic accuracy

Stool DNA and occult blood testing for screen detection of colorectal neoplasia

Objective: To compare stool DNA and fecal blood testing for detection of screen-relevant neoplasia (curable-stage cancer, high-grade dysplasia, or adenomas > 1 cm)

Method:
- 4482 average-risk adults in a blinded, multicenter, cross-sectional study

Measurements:
- Fecal blood cards (Hemoccult and HemoccultSensa)
- Stool DNA test 1 (SDT-1) was a pre-commercial 23-marker assay, and a novel test (SDT-2) targeted 3 broadly informative markers
- Criterion was standard colonoscopy

Results:
- Sensitivity for screen-relevant neoplasms was 20% by SDT-1, 11% by Hemoccult, 21% by HemoccultSensa (P=0.80)
- Sensitivity for cancer plus high-grade dysplasia did not differ among tests
- Specificity was 96% by SDT-1 compared with 98% by Hemoccult (P=0.001) and 97% by HemoccultSensa
- Stool DNA test 2 detected 46% of screen-relevant neoplasms, compared with 10% by Hemoccult (P=0.001) and 24% by HemoccultSensa
- Stool DNA test 2 detected 46% of adenomas 1 cm or larger, compared with 10% by Hemoccult (P=0.001) and 37% by HemoccultSensa (P=0.001)
- Among colonoscopically normal patients, the positivity rate was 16% with SDT-2, compared with 4% with Hemoccult (P=0.010) and 5% with HemoccultSensa (P = 0.030) (false positive)

Conclusion:
- Stool DNA test 1 provides no improvement over HemoccultSensa for detecting screen-relevant neoplasms
- Stool DNA test 2 detects significantly more neoplasms than does hemoccult or HemoccultSensa, but with more positive results in colonoscopically normal patients
Clinical performance of an automated stool DNA assay for detection of colorectal neoplasia

Aim: To optimize an automated sDNA assay and evaluate its clinical performance

POP:
- Collection of stools from 459 asymptomatic patients before screening or surveillance colonoscopies and from 544 referred patients in a blinded, multicenter, case-control study
  - Cases included:
    - 93 colorectal cancer
    - 84 advanced adenoma
    - 30 sessile serrated adenoma ≥ 1 cm
    - Controls included 155 non-advanced polyps or 641 with no colonic lesions

Methods:
- Samples were analyzed by using an automated multi-target sDNA assay to measure β-actin (a marker of total human DNA), mutant KRAS, aberrantly methylated BMP3 and NDRG4, and fecal hemoglobin

Results:
- At 90% nominal specificity, sDNA analysis identified individuals with CRC with 98% sensitivity
- Its sensitivity for advanced precancers (AA and SSA) ≥ 1 cm was 57%, for > 2 cm it was 73%, and for >3 cm it was 83%

Limitation: A key limitation of the study is the case-control design, which can overestimate test performance for CRC and advanced precursors


Multitarget stool DNA testing for colorectal-cancer screening

Methods:
- Comparison of a noninvasive, multi-target stool DNA test with a fecal immunochemical test (FIT) in persons at average risk for colorectal cancer
- The DNA test includes quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation β-actin, plus a hemoglobin immunoassay

Results:
- Sensitivity for detecting colorectal cancer was 92.3% with DNA testing and 73.8% with FIT (P<0.001)
- The sensitivity for detecting advanced precancerous lesions was 42.4% with DNA testing and 23.8% with FIT (P<0.001)
- Specifcity with DNA testing and FIT were 84.4% and 94.9% respectively, among participants with nonadvanced or negative findings (P<0.001) and 99.8% and 96.4%

Conclusion:
- DNA testing detected significantly more cancers than did FIT but had more false positive results

Fecal DNA Testing -2014

• Presently, fecal DNA’s intended use would optimally be for the individuals who are not eligible, unwilling or unable to be screened by one of the more invasive screening tests

Barriers for adoptive general use of fecal DNA

• Unknown diagnostic accuracy
• Current lack of standardization or optimization of fecal DNA panels
• Unclear ease of use of test
• Unclear acceptability of fecal DNA testing
• An adequate stool sample must be obtained and packaged with appropriate preservative agents for shipping to the laboratory

Future: Fecal DNA testing will likely replace FIT as its sensitivity and accuracy elevate and its cost comes down

Screening rationale

- Most colorectal cancers arise from adenomatous polyps that increase in size and then develop dysplasia and cancer
- Progression from adenoma to carcinoma is believed to take at least 10 years
- 2/3rds of polyps are adenomas
- More common in men (25%) than women (15%)
- Prevalence increases with age
- Sessile serrated polyps are more common on R>L
  - Their neoplastic progression is through CIMP pathway which may be more rapid than for adenoma
- Slow transition from polyps to colorectal cancer allows opportunities to prevent cancer by removing polyps and to prevent cancer death by removing early cancers

Factors favoring progression of colonic adenomas to colon cancer

- Larger than 1 cm
- Contains villous histology
- High-grade dysplasia
- Adenoma-to-carcinoma sequence in colon cancer is based on the stepwise accumulation of specific genetic alterations that parallel the histopathologic progression from pre-neoplasia to neoplasia
  
Now: molecular diagnostic assays that detect gene mutations in tumor cells sloughed into stool

2012 Recommendations for surveillance and screening intervals with baseline average risk

<table>
<thead>
<tr>
<th>Baseline Colonoscopy: Most Advanced Finding(s)</th>
<th>Recommended Surveillance Interval (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyps</td>
<td>10</td>
</tr>
<tr>
<td>Small (&lt;10 mm) hyperplastic polyps in rectum or sigmoid</td>
<td>10</td>
</tr>
<tr>
<td>1-2 small (&lt;10 mm) tubular adenomas (Low)</td>
<td>5-10</td>
</tr>
<tr>
<td>3-10 tubular adenomas (High)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 adenomas</td>
<td>&lt;3</td>
</tr>
<tr>
<td>One or more tubular adenomas ≥ 10 mm</td>
<td>3</td>
</tr>
<tr>
<td>One or more villous adenomas</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Adenoma with high grade dysplasia (HGD)</td>
<td>3</td>
</tr>
</tbody>
</table>
**2012 Recommendations for surveillance and screening intervals with baseline average risk**

<table>
<thead>
<tr>
<th>Baseline Colonoscopy: Most Advanced Finding(s)</th>
<th>Recommended Surveillance Interval (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serrated lesions</td>
<td></td>
</tr>
<tr>
<td>Sessile serrated polyp(s) &lt;10mm with no dysplasia</td>
<td>5</td>
</tr>
</tbody>
</table>


**Recommendations for polyp surveillance after first surveillance colonoscopy is based on what was found**

<table>
<thead>
<tr>
<th>Baseline Colonoscopy</th>
<th>First Surveillance</th>
<th>Interval for Second Surveillance (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk adenomas (LRA)</td>
<td>HRA</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>LRA</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>No adenoma</td>
<td>10</td>
</tr>
<tr>
<td>High-risk adenomas (HRA)</td>
<td>HRA</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>LRA</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>No adenoma</td>
<td>5</td>
</tr>
</tbody>
</table>


**Risk for developing colorectal cancer in people with adenomas**

<table>
<thead>
<tr>
<th>Follow-up Colonoscopy</th>
<th>Low risk - One or two adenomas smaller than 10 mm</th>
<th>Intermediate risk - Three or four adenomas smaller than 10 mm or One or two adenomas if one is 10 mm or larger</th>
<th>High Risk - Five or more adenomas smaller than 10 mm or Three or more adenomas if one is 10 mm or larger</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 years</td>
<td>3 years</td>
<td>1 year</td>
</tr>
</tbody>
</table>

The appropriate colonoscopy surveillance strategy to people with adenomas based on their risk of developing colorectal cancer determined at initial adenoma removal

**Low risk: consider colonoscopy at 5 years**
- If the colonoscopy is negative (i.e., no adenomas are found) stop surveillance
- If low risk, consider the next colonoscopy at 5 years (with follow-up surveillance as for low risk)
- If intermediate risk, offer the next colonoscopy at 3 years (with follow-up surveillance as for intermediate risk)
- If high risk, offer the next colonoscopy at 1 year (with follow-up surveillance as for high risk)

**Intermediate risk: Offer colonoscopy at 3 years**
- If the colonoscopy is negative, offer the next colonoscopy at 3 years
- Stop surveillance if there is a further negative result
- If low or intermediate risk, offer the next colonoscopy at 3 years (with follow-up surveillance as for intermediate risk)
- If high risk, offer the next colonoscopy at 1 year (with follow-up surveillance as for high risk)

**High Risk: offer colonoscopy at 1 year**
- If the colonoscopy is negative, or low or intermediate risk, offer the next colonoscopy at 3 years (with follow-up surveillance as for intermediate-risk)
- If high risk, offer the next colonoscopy at 1 year (with follow-up surveillance as for high risk)

THANK YOU