COLORECTAL CANCER SCREENING

Michael Passarella, M.D.
October 28, 2017
Principles of a Good Screening Program

- **The Disease should:**
  - Constitute a significant public health burden
  - Have a well defined target (or “at risk”) population
  - Have a well understood natural history
  - Have a latent period before clinical deterioration
  - Have a readily available treatment
    - With potential for cure if detected early

- **The proposed screening test should:**
  - Be safe and acceptable for the general population
  - Be widely available and accessible to the general population
  - Be capable of detecting a majority of disease in its pre-clinical state
  - Be reasonable in cost
  - Lead to demonstrated improvements in health

- **The overall benefits of screening should outweigh the harms**
Natural History of Colorectal Cancer

Normal Colon

Early

Intermediate

Adenoma (pre-cancer)

Late

Cancer

~ 10 – 15 years
Genetic and Molecular Epidemiology of Colorectal Cancer

 Targets in Colorectal Tumorigenesis

DNA Mismatch Repair Enzymes (hMSH2, hMLH1 etc)

5q Mutation or Loss APC

DNA Methylation Changes

12p Mutation K-ras

18q Loss SMAD4/DPC4

17p Loss p53

Other Targets including TGFβRII

Other Alterations

Normal Epithelium

Hyperproliferating Epithelium

Early Adenoma

Intermediate Adenoma

Late Adenoma

Carcinoma

After Fearon and Vogelstein, 1990

Figure 9-5. Hypothesized genes that are mutated in the pathway to colorectal cancer.
Outline: What are the options?

- Stool-Based Tests
  - Fecal Occult Blood Testing (FOBT)
  - Fecal Immunochemical Testing (FIT)
  - Stool DNA Testing (sDNA)
- Direct visualization
  - Computed Tomography Colonography (CTC)
  - Flexible Sigmoidoscopy (FS)
  - Colonoscopy
- Future Studies
- Summary
Stool-Based Tests
Fecal Occult Blood Test (FOBT)

- 2 fecal samples from each of 3 separate specimens are required
- Positive test relies on the pseudoperoxidase activity of heme, which facilitates oxidation of guaiac when hydrogen peroxide is added
- Susceptible to interference from many foods and drugs
Fecal Occult Blood Testing (FOBT)

- There have been 5 RCTs (n=442,088) that evaluated annual or biennial screening with Hemoccult II for the prevention of CRC mortality.
- All five trials included varying rounds of screening with guaiac-based FOBT (n = 419,966) and showed an overall reduction in CRC-specific mortality:
  - RR, 0.91; 95% CI, 0.84-0.98 at 19.5 years
  - RR, 0.78; 95% CI, 0.65-0.93, at 30 years
- Only one RCT by Mandel et al. published in NEJM in 2000, showed a decrease in CRC incidence associated with FOBT screening.
Long-Term Mortality after FOBT Screening for Colorectal Cancer

- Initial results were published in 2000, and long-term follow-up results were published in 2013
- The rate of response to the annual follow-ups was > 99% in all three groups
- Through 30-years of follow-up, 33,020 participants (70.9%) died
  - 732 deaths (1.5% of total study participants) were attributable to CRC
  - 200 patients (1.3%) died from CRC in the annual screening group
  - 237 patients (1.5%) died from CRC in the biennial screening group
  - 295 patients (1.9%) died from CRC in the control group
- FOBT Screening reduced CRC mortality through 30-years of follow-up
  - Annual Screening (RR: 0.68; 95% CI, 0.56 to 0.82)
  - Biennial Screening (RR: 0.78; 95% CI, 0.65 to 0.93)

Shaukat, Aasma et al. Long-Term Mortality after Screening for Colorectal Cancer. NEJM. May 2013
Cumulative CRC Mortality at 30 Yr

Cumulative Colorectal-Cancer Mortality at 30 Yr (95% CI)
- Control: 0.03 (0.03–0.03)
- Biennial screening: 0.02 (0.02–0.03)
- Annual screening: 0.02 (0.02–0.02)

Years since Randomization

No. at Risk
- Control: 14,497 13,103 11,320 9157 6741 4450
- Biennial screening: 14,635 13,243 11,445 9323 6802 4583
- Annual screening: 14,658 13,294 11,437 9219 6802 4498
Fecal Occult Blood Testing (FOBT)

**Advantages**

- Five different RCTs demonstrate reduction in CRC mortality in average risk patients
- One RCT with reduction in CRC incidence
- Non-invasive test
- Inexpensive
- Can administer at home

**Disadvantages**

- Does not decrease all-cause mortality
- Requires 3 separate stools samples
- Requires strict dietary and medication modifications prior to testing
- Requires subsequent colonoscopy for positive test (~30%)
- Low rate of detecting advanced adenomas
Fecal Immunochemical Test (FIT)
Fecal Immunochemical Tests (FIT)

- Immunoassay specific for human hemoglobin, forming an antibody-antigen complex with its globin moiety
- FIT tests only detect *human* hemoglobin that occurs in the lower GI tract (globin is digested with UGIB)
- Foods with peroxidase activity do not produce a positive reaction
- Both qualitative and quantitative FITs are commercially available
Fecal Immunochemical Testing (FIT)

- To date, there are no RCTs that demonstrate FIT is superior to FOBT (or to no screening) in terms of reducing CRC incidence/mortality in average risk persons.
- 12 RCTs exist that examine the comparative effectiveness of FIT compared to other screening tests.
- These trials were primarily designed to assess adherence of testing and are not powered to detect differences in CRC mortality or incidence.
- Test accuracy studies have revealed FIT superior to FOBT in terms of sensitivity/specificity.
- Evidence-based reasoning supports that screening with FIT should therefore result in similar (or better) reductions in CRC incidence/mortality.
Sensitivity/Specificity for CRC: FIT vs. FOBT

**FOBT**
- Hemoccult Sensa is more sensitive than Hemoccult II, although it has lower specificity
- Sensitivity for CRC:
  - Hemoccult Sensa: 64-80%
  - Hemoccult II: 25-38%
- Specificity for CRC:
  - Hemoccult Sensa: 87-90%
  - Hemoccult II: 98-99%

**FIT**
- OC-Light (qualitative) has similar sensitivity and specificity compared with OC-Micro/Sensor (quantitative)
- Sensitivity for CRC (best):
  - OC-Light: 79-88%
  - OC-Micro/Sensor: 73-86%
- Specificity for CRC:
  - OC-Light: 91%
  - OC-Micro/Sensor: 91%
Comparison – FOBT vs. FIT

**FOBT**
- Demonstrated CRC mortality reduction in 5 RCTs
- Demonstrated CRC incidence reduction in one RCT
- Less expensive

**FIT**
- FIT requires fewer stool samples (1 vs. 3)
- Does not require dietary or medication restrictions
- Qualitative or quantitative
- RCTs demonstrate increased adherence compared to FOBT
- Increased sensitivity for CRC and AA compared to FOBT
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Stool DNA (sDNA) Testing
Stool DNA Testing (sDNA)

- 4 studies have evaluated the performance of sDNA testing for CRC in average risk adults
  - No RCTs have been conducted regarding CRC incidence/mortality
- The sDNA tests used in three of the four studies are no longer offered by the manufacturer
- The original 3 studies resulted in rather poor sensitivity for CRC (range 25% to 51.6%) and AA (15.1% to 19%)
- In 2008, the USPSTF concluded there was “insufficient evidence regarding the clinical accuracy for sDNA testing” for CRC
- The manufacturer reconfigured its sDNA test and combined it with FIT testing for human hemoglobin
  
  Cologuard®

sDNA Testing

- Cologuard®, is currently the only sDNA test available on the market
- It relies on genetic mutations that are acquired during carcinogenesis to be detected in the stool from DNA shed by colorectal neoplasms
- Cologuard® combines testing stool for DNA mutations and/or methylation markers (using a gene amplification technique) with testing for human hemoglobin with FIT
  - Point mutations in the KRAS gene and beta-actin gene
  - Hypermethylation of the promoter regions of BMP3 and NDRG4 genes
- Requires a full stool sample be collected for analysis
- Since the 2008 USPSTF recommendation, one additional diagnostic accuracy study for sDNA has been published
A cross-sectional study published in the NEJM in 2014 that compared sDNA (Cologuard®) with FIT in detection of CRC in average risk participants

Investigators enrolled participants who were scheduled to undergo screening colonoscopy at one of 90 sites throughout the U.S. and Canada between June 2011 and November 2012

Target population included asymptomatic, average risk participants, between the ages of 50-84 years of age

- Enrollment was weighted toward persons >65 years of age to increase prevalence of cancer

They excluded participants who had personal or family history of CRC, digestive cancer, or IBD; had undergone colonoscopy within the prior 9-years or a DCBE/CTC/Sigmoidoscopy in prior 5-years; had positive FOBT/FIT within prior 6-months; had undergone colon resection; had overt rectal bleeding in prior month; or were unable to provide consent
Table 1. Sensitivity and Specificity of the Multitarget Stool DNA Test and the Fecal Immunochemical Test (FIT) for the Most Advanced Findings on Colonoscopy.

<table>
<thead>
<tr>
<th>Most Advanced Finding</th>
<th>Colonoscopy (N=9989)</th>
<th>Multitarget DNA Test (N=9989)</th>
<th>FIT (N=9989)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>Positive Results</td>
<td>Sensitivity (95% CI)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>65</td>
<td>60</td>
<td>92.3 (83.0–97.5)</td>
</tr>
<tr>
<td>Stage I to III*</td>
<td>60</td>
<td>56</td>
<td>93.3 (83.8–98.2)</td>
</tr>
<tr>
<td>Colorectal cancer and high-grade dysplasia</td>
<td>104</td>
<td>87</td>
<td>83.7 (75.1–90.2)</td>
</tr>
<tr>
<td>Advanced precancerous lesions†</td>
<td>757</td>
<td>321</td>
<td>42.4 (38.9–46.0)</td>
</tr>
<tr>
<td>Nonadvanced adenoma</td>
<td>2893</td>
<td>498</td>
<td>17.2 (15.9–18.6)</td>
</tr>
<tr>
<td>All nonadvanced adenomas, non-neoplastic findings, and negative results on colonoscopy</td>
<td>9167</td>
<td>1231</td>
<td>86.6 (85.9–87.2)</td>
</tr>
<tr>
<td>Negative results on colonoscopy</td>
<td>4457</td>
<td>455</td>
<td>89.8 (88.9–90.7)</td>
</tr>
</tbody>
</table>

* These stages of colorectal cancer, as defined by the system recommended by the American Joint Committee on Cancer, are associated with an increased rate of cure.
† Advanced precancerous lesions include advanced adenomas and sessile serrated polyps measuring 1 cm or more.
Advanced Precancerous Lesions (APL)

- 757 cases of APL
  - sDNA picked up 321 (42.4%)
- 39 cases of HGD
  - sDNA picked up 69.2%
- 99 cases of SSA > 1cm
  - sDNA picked up 42%
- Sensitivity of sDNA was worse for detecting proximal APL with sensitivity of only 33.2% (95% CI, 28%-37%)

### Stool DNA Testing - Conclusion

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Only requires testing every 1-3 years</td>
<td>• No RCTs with mortality endpoints</td>
</tr>
<tr>
<td>• Non-invasive</td>
<td>• Requires collection of a full stool sample</td>
</tr>
<tr>
<td>• Does not require dietary or medication restrictions</td>
<td>• Much more expensive than other stool-based tests</td>
</tr>
<tr>
<td>• Superior sensitivity at detecting CRC and advanced adenomas compared to other stool-based tests (FIT)</td>
<td>• Implications of “false-positive” test results are unclear (lower specificity)</td>
</tr>
</tbody>
</table>
Direct-Visualization Tests
CT Colonography (CTC)

- There are no RCTs of screening CTC related to CRC incidence or mortality
  - The case for CTC effectiveness rests on its test sensitivity and specificity being comparable to other tests, such as sigmoidoscopy, that are established by RCT
- There are nine fair-to-good quality prospective diagnostic accuracy studies evaluating CTC (n=6497) in which all persons also received a colonoscopy
  - The largest study was a multicenter study (n=2531) published in NEJM in 2008
- All nine studies recruited similar populations, asymptomatic, average-risk adults age 50 years or older
- The baseline prevalence of cancer in the included populations ranged from 0.16 percent to 1.1 percent
- Only three studies used the best choice of reference standard (i.e., colonoscopy with segmental unblinding (CTC-enhanced colonoscopy)
- 7 of these studies utilized bowel prep (n=5,328), while two (n=1,169) did not with marked decline in test sensitivity
- Only 3 studies (n=1,044) reported sensitivity to detect advanced adenomas or polyps < 6mm

CT Colonography (CTC)

- The test positivity for having at least one lesion > 5mm on screening CTC ranged from 10 to 30%
- Overall, included studies were not powered to estimate test performance in detecting CRC because of low numbers of cancers in these studies
- In the 7 studies utilizing bowel prep (n=5328), only 20 CRCs were detected (0.4%)
  - 19/20 were detected by CTC, with a 10mm adenocarcinoma in the low rectum representing the only malignancy missed by CTC
- The per-person sensitivity and specificity for detecting:
  - Adenomas > 6mm
    - Pooled estimate: 86.5% and 94.4%, respectively
  - Adenomas > 10mm
    - Pooled estimate: 89.2% and 94.4%, respectively
  - Advanced Adenomas (>10mm, HGD, villous histology)
    - Ranged from 87.5-100% and 39.4-87.1%
- CTC has improved sensitivity in detection of non-advanced and advanced adenomas compared to stool-based tests and is currently an option for CRC screening recommended by the USPSTF

## CT Colonography: Conclusion

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Less invasive compared to colonoscopy</td>
<td>• Expensive</td>
</tr>
<tr>
<td>• No anesthesia required</td>
<td>• Reading takes place after the patient has been discharged</td>
</tr>
<tr>
<td>• Does not require IV contrast</td>
<td>• Requires colonoscopy and repeat prep for positive findings (~30%)</td>
</tr>
<tr>
<td>• Similar sensitivities to colonoscopy in regards to large adenomas (and likely colon cancers)</td>
<td>• Majority of post-imaging referrals are for non-significant findings</td>
</tr>
<tr>
<td>• Testing only required every 5-years</td>
<td>• Extracolonic findings are difficult to interpret</td>
</tr>
<tr>
<td></td>
<td>• Flat adenomas are missed more often than with colonoscopy</td>
</tr>
<tr>
<td></td>
<td>• Cumulative radiation exposure</td>
</tr>
</tbody>
</table>
Flexible Sigmoidoscopy (FS)
Screening Flexible Sigmoidoscopy

• There are four fair-to-good quality RCTs evaluating the effectiveness of FS for CRC screening (mortality/incidence)
• Only one of these trials was conducted in the U.S.
  • Norway, Italy, and United Kingdom
• All trials started in the 1990s and recruited average-risk adults between the ages of 50-74
  • Mean age across the trials was 56-60
• All trials included an even mix of men and women
• Only the U.S. trial reported race/ethnicity of participants
  • This trial included 14% nonwhite participants
• Only two trials reported underlying family history of CRC
  • ~10% in these two trials
• The baseline prevalence of CRC in the 4 trials was 1.5%
Colorectal-Cancer Incidence and Mortality with Screening Flexible Sigmoidoscopy

- RCT published in NEJM in 2012 randomly assigned 154,900 participants to screening FS (plus repeat FS at 3 or 5 years) vs. usual care
  - Of the 77,445 participants assigned to FS group, 83.5% underwent baseline FS with 54% adhering to f/u FS
  - After median f/u 11.9 years, there were 1012 CRC cases (1.3%) in the intervention group as compared to 1287 cases (1.6%) in the control group (RR, 0.79; 95% CI: 0.72-0.85)
  - 252 patients (0.3%) died from CRC in FS group compared to 341 (0.4%) in the control group (RR, 0.74; 95% CI: 0.63-0.87)
  - Mortality from CRC was halved for distal cancers (87 vs. 175 deaths) but unchanged for proximal cancers (143 vs. 147 deaths)
- **Screening with FS is associated with a significant decrease in CRC incidence (in both distal and proximal colon) and mortality (distal colon only)**

Colonoscopy
Screening Colonoscopy

- To date, there are no RCTs evaluating the efficacy of screening colonoscopy
- Completed trials of flexible sigmoidoscopy provides indirect evidence that colonoscopy would produce similar reductions in CRC incidence/mortality
- There is one fair-to-good quality prospective cohort study (n=88,902) that analyzed the association of screening colonoscopy with the risk of CRC over 22 years
- The study analyzed prospectively-collected data from two large cohorts; the Nurses’ Health Study (NHS) and the Health Professionals Follow-up Study (HPS)
  - NHS included 121,700 female nurses, 30-55 years of age at enrollment in 1976
  - HPS included 51,529 male health professionals, 40-75 years of age at enrollment in 1986
- Results were published in the NEJM in 2013
Long-term CRC incidence and mortality after lower endoscopy

- Among 88,902 participants followed over a 22-year period, they found 1,815 incident CRCs (2%) and 474 deaths from CRC.
- Compared to no endoscopy, those with endoscopy had a Hazard Ratio (HR) for a diagnosis of CRC of:
  - 0.60 (CI, 0.53-0.68) after negative sigmoidoscopy
  - 0.44 (CI, 0.38-0.52) after negative colonoscopy
- Multivariate HR for CRC mortality was:
  - 0.59 (CI, 0.45-0.76) after screening sigmoidoscopy
  - 0.32 (CI, 0.24-0.45) after screening colonoscopy
- Reduced mortality from proximal CRC was observed after screening colonoscopy (HR: 0.47; CI, 0.29-0.76) but not after sigmoidoscopy (HR: 1.04; CI, 0.73-1.48)
- Colonoscopy and FS are associated with a reduced incidence/mortality of distal CRCs; but only colonoscopy is associated with reduced mortality from proximal CRCs
In 2012, Zauber et al. published a follow-up analysis of the NPS, which included all patients prospectively referred for initial colonoscopy (between 1980-1990) who had adenomatous polyps removed via polypectomy.

- Using the National Death Index, cause of death was determined for each participant in the study with an average follow-up time of 23 years.
- Mortality from CRC among patients with adenomas removed was compared with the expected incidence-based mortality from CRC in the general population, based on SEER database.
- Among 2602 patients with adenomatous polyps removed, 1246 had died from any cause and 12 had died from CRC during the 23-year follow-up period.
- Given an estimated 25.4 expected deaths from CRC in the general population, the standardized incidence-based mortality was 0.47 (95% CI, 0.26-0.80) with colonoscopic polypectomy, suggesting a 53% reduction in CRC mortality.

Colonoscopic removal of adenomatous polyps reduces mortality from CRC.

Table 3. Deaths from Colorectal Cancer in the Adenoma Cohort, as Compared with Incidence-Based Mortality from Colorectal Cancer in the General Population.*

<table>
<thead>
<tr>
<th>Follow-up Time</th>
<th>Adenoma Cohort</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Person-Years at Risk</td>
</tr>
<tr>
<td>All</td>
<td>2602</td>
<td>37,073</td>
</tr>
<tr>
<td>&lt;10 yr</td>
<td>2602</td>
<td>22,903</td>
</tr>
<tr>
<td>≥10 yr</td>
<td>2031</td>
<td>14,170</td>
</tr>
</tbody>
</table>

Colonoscopy

Advantages

• Associated with significantly lower rates of CRC incidence/mortality in both distal and proximal cancers
• Can provide therapeutic as well as screening purposes in same procedure
• Gold standard in regards to CRC and AA detection
• Only required every 10-years

Disadvantages

• Most expensive
• Adverse events are the highest of all screening options
• Currently, no RCTs supporting its benefit
• Requires some form of sedation/anesthesia
• Invasive
• Requires bowel prep
ACG CRC Screening Guidelines

### Preferred CRC screening recommendations

- Cancer prevention tests should be offered first. The preferred CRC prevention test is colonoscopy every 10 years, beginning at age 50. (Grade 1 B) Screening should begin at age 45 years in African Americans (Grade 2 C)

- Cancer detection test. This test should be offered to patients who decline colonoscopy or another cancer prevention test. The preferred cancer detection test is annual FIT for blood (Grade 1 B)

### Alternative CRC prevention tests

- Flexible sigmoidoscopy every 5–10 years (Grade 2 B)
- CT colonography every 5 years (Grade 1 C)

### Alternative cancer detection tests

- Annual Hemoccult Sensa (Grade 1 B)
- Fecal DNA testing every 3 years (Grade 2 B)
<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults aged 50 to 75 years</td>
<td>The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years. The risks and benefits of different screening methods vary. See the Clinical Considerations section and the Table for details about screening strategies.</td>
<td>A</td>
</tr>
</tbody>
</table>
| Adults aged 76 to 85 years  | The decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient’s overall health and prior screening history.  
  • Adults in this age group who have never been screened for colorectal cancer are more likely to benefit.  
  • Screening would be most appropriate among adults who 1) are healthy enough to undergo treatment if colorectal cancer is detected and 2) do not have comorbid conditions that would significantly limit their life expectancy. | C     |
USMSTF Recommendations

<table>
<thead>
<tr>
<th>Tier 1</th>
</tr>
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<tbody>
<tr>
<td>Colonoscopy every 10 years</td>
</tr>
<tr>
<td>Annual fecal immunochemical test</td>
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<table>
<thead>
<tr>
<th>Tier 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT colonography every 5 years</td>
</tr>
<tr>
<td>FIT–fecal DNA every 3 years</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 10 years (or every 5 years)</td>
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</table>

<table>
<thead>
<tr>
<th>Tier 3</th>
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<tbody>
<tr>
<td>Capsule colonoscopy every 5 years</td>
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<table>
<thead>
<tr>
<th>Available tests not currently recommended</th>
</tr>
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<tr>
<td>Septin 9</td>
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Summary:
Rationale for CRC Screening

• CRC is common with high burden of disease
• CRC has precursor lesions that can be detected with screening
• Survival largely depends on the stage at time of diagnosis
• Screening can affect both primary and secondary prevention
  • 1°: Finding precancerous lesions that could later become malignant
  • 2°: Detecting early cancers that can be more effectively treated
• RCTs (see later) have demonstrated that screening for CRC has reduced disease incidence and disease-specific mortality
• The decrease in CRC incidence and mortality over the past two decades correlates with an increase in screening rates from <25% in the 1980s to ~52% in 2002 and a ~65% in 2012
• Screening tests currently used in the US that have evidence to support their use include high sensitivity gFOBT, FIT, FS, and colonoscopy.73