The New Grade A: USPSTF Updated Colorectal Cancer Screening Guidelines, What does it all mean?

Robert A. Smith, PhD
Cancer Control, Department of Prevention and Early Detection
Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology.++


Annals of Internal Medicine

Screening for Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement

U.S. Preventive Services Task Force.*


METHODS: To update its recommendation, the USPSTF commissioned 2 articles: (a) a targeted systematic evidence review on 4 selected questions relating to task characteristics and benefits and harms of screening technologies, and (b) a decision-analytic modeling analysis using population modeling techniques to compare the expected health outcomes and resource requirements of available screening modalities when used on a programmatic scale over time.

Recommendations: The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy or colonoscopy in adults, beginning at age 50 years and continuing every 10 years. The benefits and harms of these screening methods vary. Clinicians and policymakers should understand the evidence but individualize decision-making in the specific patient or situation.

CLINICAL GUIDELINES

The USPSTF recommends against screening for colorectal cancer in adults age 76 or 85 years. There may be considerations that support colorectal screening in an individual patient. This is C recommendation.

The USPSTF recommends against screening for colorectal cancer in adults older than age 85 years. This is a D recommendation.

The USPSTF concludes that the evidence is insufficient to assess the balance of good and harms of computed tomographic angiography and fecal DNA testing as screening modalities for colorectal cancer (C recommendation).

SUMMARY OF RECOMMENDATION AND EVIDENCE

The USPSTF recommends colorectal cancer testing fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing every 10 years. The risks and benefits of these screening methods vary. See the Rationale and Clinical Considerations sections for comparison of the risks and benefits of different screening regimens, as well as the specific insights for different screening methods. This is an A recommendation.

Annals of Internal Medicine

www.aim.org
CRC Screening in Average Risk Adults: Update 2008

Recommendations in red represent differences

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>ACS, USMSTF, ACR</th>
<th>USPSTF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stool Testing</strong></td>
<td>Annual screening with high sensitivity (HS) gFOBT or FIT, or mtsDNA every 3 years</td>
<td>Annual screening with high sensitivity gFOBT or FIT sDNA, insufficient evidence</td>
</tr>
<tr>
<td>• gFOBT</td>
<td>Low sensitivity gFOBT not recommended</td>
<td></td>
</tr>
<tr>
<td>• FIT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• mtsDNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flexible sigmoidoscopy</strong></td>
<td>Screening every 5 years, with annual gFOBT or FIT is an option</td>
<td>Screening every 5 years, with addition of gFOBT or FIT every 3 years</td>
</tr>
<tr>
<td><strong>Colonoscopy</strong></td>
<td>Screening every 10 years</td>
<td>Screening every 10 years</td>
</tr>
<tr>
<td><strong>CT Colonography</strong></td>
<td>Screening every 5 years</td>
<td>Insufficient evidence (I)</td>
</tr>
</tbody>
</table>
• On June 20, 2016, the USPSTF released updated CRC screening recommendations

• The recommendations covered colorectal cancer screening with FOBT (gFOBT, FIT, and FIT-DNA), endoscopy (colonoscopy and flexible sigmoidoscopy), and CT colonography

• Two tests not endorsed in the draft recommendations released in 2015 (FIT-DNA and CT colonography) were endorsed in the 2016 final recommendations.
In the current recommendation, instead of emphasizing specific screening approaches, the USPSTF has instead chosen to highlight that there is convincing evidence that colorectal cancer screening substantially reduces deaths from the disease among adults aged 50 to 75 years and that not enough adults in the United States are using this effective preventive intervention.
**USPSTF CRC Screening Recommendations, 2016— How does these changes compare with the 2008 ACS guideline?**

<table>
<thead>
<tr>
<th>Screening Method</th>
<th>Frequency</th>
<th>Evidence of Efficacy</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stool-Based Tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gFOBT</td>
<td>Every year</td>
<td>RCTs with mortality end points: High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II)</td>
<td>Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)</td>
</tr>
<tr>
<td>FIT&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Every year</td>
<td>Test characteristic studies: Improved accuracy compared with gFOBT, Can be done with a single specimen</td>
<td>Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)</td>
</tr>
<tr>
<td>FIT-DNA</td>
<td>Every 1 or 3 y&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Test characteristic studies: Specificity is lower than for FIT, resulting in more false-positive results, more diagnostic colonoscopies, and more associated adverse events per screening test. Improved sensitivity compared with FIT per single screening test</td>
<td>There is insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy; may potentially lead to overly intensive surveillance due toprovider and patient concerns over the genetic component of the test</td>
</tr>
</tbody>
</table>

| **Direct Visualization Tests** | | | |
| Colonoscopy<sup>c</sup> | Every 10 y | Prospective cohort study with mortality end point | Requires less frequent screening. Screening and diagnostic follow-up of positive findings can be performed during the same examination |
| CT colonography<sup>e</sup> | Every 5 y | Test characteristic studies | There is insufficient evidence about the potential harms of associated extracolonic findings, which are common |
| Flexible sigmoidoscopy | Every 5 y | RCTs with mortality end points: Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies | Test availability has declined in the United States |
| Flexible sigmoidoscopy with FIT<sup>c</sup> | Flexible sigmoidoscopy every 10 y plus FIT every year | RCT with mortality end point (subgroup analysis) | Test availability has declined in the United States. Potentially attractive option for patients who want endoscopic screening but want to limit exposure to colonoscopy |

ACS endorses screening Q 3 yrs.

Same

ACS does not emphasize combined FSIG/FOBT
AAFP Releases Updated CRC Screening Recommendations

*Academy Statement Includes Evidence-based Suggestions for Specific Tests*

August 31, 2016 04:37 pm  [Chris Crawford](https://www.aafp.org/news/2016/08/31/AAFP Releases Updated CRC Screening Recommendations.html) — On June 15, the U.S. Preventive Services Task Force (USPSTF) published its [final recommendation statement](https://www.uspreventiveservicestaskforce.org) and [evidence summary](https://www.uspreventiveservicestaskforce.org) on screening for colorectal cancer and found that "convincing evidence" supported screening adults ages 50-75 — an "A" recommendation.

The AAFP’s Commission on Health of the Public and Science’s Subcommittee on Clinical Preventive Services reviewed the USPSTF’s recommendation and agreed that screening this age group for colorectal cancer should be recommended. However, in the [AAFP's final recommendation statement](https://www.aafp.org/news/2016/08/31/AAFP Releases Updated CRC Screening Recommendations.html), the subcommittee made this a "D" recommendation and also differed from the task force on suggestions for recommended screening tests.

In addition, the AAFP agreed with the USPSTF’s recommendation that the decision to screen for colorectal cancer in adults ages 76-85 be an individualized one, taking into account the patient’s overall health and...
AAFP CRC Screening Guidelines, 2016

- While the USPSTF gave CRC Screening an “A” rating, the AAFP gave it a “B” rating.
- AAFP only recommends FIT, Flexible sigmoidoscopy, and colonoscopy

Colorectal Cancer Screening, Adults

GRADE: B RECOMMENDATION

The AAFP recommends screening for colorectal cancer with fecal immunochemical tests, flexible sigmoidoscopy, or colonoscopy starting at age 50 years and continuing until age 75 years. The risks, benefits, and strength of supporting evidence of different screening methods vary. (2016)
AAFP CRC Screening Guidelines, 2016

- CTC and MT-sDNA are not recommended due to insufficient evidence on harms
- Age to stop is similar to the USPSTF

GRADE: C RECOMMENDATION

The AAFP *recommends* that the decision to screen for colorectal cancer in adults aged 76 to 85 years be an individual one, taking into account the patient's overall health and prior screening history. (2016)

[Grade Definition](www.uspreventiveservicestaskforce.org)

GRADE: D RECOMMENDATION

The AAFP *recommends against* screening for colorectal cancer in adults older than 85 years. (2016)
We are surprised by the latest update of the recommendations for colorectal cancer screening from the U.S. Preventive Services Task Force (USPSTF) (1). Contrary to the principles of evidence-based medicine, the guidelines provided equally strong recommendations for tests with very different quality of evidence for benefits and harms.
### Table. Colorectal Cancer Screening Strategies Recommended by the USPSTF and Their Recommended Use in Italy, Norway, Poland, Spain, and Sweden

<table>
<thead>
<tr>
<th>Screening Strategies Recommended by the USPSTF</th>
<th>Recommended in Italy, Norway, Poland, Spain, and Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>FOBT</td>
<td>All countries</td>
</tr>
<tr>
<td>FIT</td>
<td>All countries</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Poland</td>
</tr>
<tr>
<td>Sigmoidoscopy alone</td>
<td>Italy and Norway</td>
</tr>
<tr>
<td>Sigmoidoscopy plus FOBT/FIT</td>
<td>-</td>
</tr>
<tr>
<td>Computed tomography colonography</td>
<td>-</td>
</tr>
<tr>
<td>FIT DNA testing</td>
<td>-</td>
</tr>
</tbody>
</table>

FIT = fecal immunochemical testing; FOBT = fecal occult blood testing; USPSTF = U.S. Preventive Services Task Force.
Benefits, Harms, and Burden of Colorectal Screening Strategies Over a Lifetime (1)

Benefit: Life-years gained per 1000 individuals screened

<table>
<thead>
<tr>
<th>Screening Method and Frequency</th>
<th>Model Estimates, Life-Years Gained per 1000 Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Middle</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 5 y</td>
<td>221</td>
</tr>
<tr>
<td>FIT-DNA every 3 y</td>
<td>226</td>
</tr>
<tr>
<td>FIT every year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>244</td>
</tr>
<tr>
<td>HSGFOBT every year</td>
<td>247</td>
</tr>
<tr>
<td>CT colonography every 5 y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>248</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 10 y plus FIT every year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>256</td>
</tr>
<tr>
<td>FIT-DNA every year</td>
<td>261</td>
</tr>
<tr>
<td>Colonoscopy every 10 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>270</td>
</tr>
</tbody>
</table>

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Benefits, Harms, and Burden of Colorectal Screening Strategies Over a Lifetime (2)

Benefit: CRC deaths averted per 1000 individuals screened

<table>
<thead>
<tr>
<th>Screening Method and Frequency</th>
<th>Averted per 1000 Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Middle</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 5 y</td>
<td>20</td>
</tr>
<tr>
<td>FIT-DNA every 3 y</td>
<td>20</td>
</tr>
<tr>
<td>FIT every year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22</td>
</tr>
<tr>
<td>HSgFOBT every year</td>
<td>22</td>
</tr>
<tr>
<td>CT colonography every 5 y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 10 y plus FIT every year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23</td>
</tr>
<tr>
<td>FIT-DNA every year</td>
<td>23</td>
</tr>
<tr>
<td>Colonoscopy every 10 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24</td>
</tr>
</tbody>
</table>

CRC Deaths Averted per 1000 Screened
Harms: Complications (gastrointestinal and cardiovascular events) of colorectal cancer screening and follow-up testing per 1000 individuals screened

<table>
<thead>
<tr>
<th>Screening Method and Frequency</th>
<th>Model Estimates, Complications per 1000 Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model estimates: Complications per 1000 Screened</td>
<td>Middle</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 5 y</td>
<td>10</td>
</tr>
<tr>
<td>FIT-DNA every 3 y</td>
<td>9</td>
</tr>
<tr>
<td>FIT every year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10</td>
</tr>
<tr>
<td>HsFOBT every year</td>
<td>11</td>
</tr>
<tr>
<td>CT colonography every 5 y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 10 y plus FIT every year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11</td>
</tr>
<tr>
<td>FIT-DNA every year</td>
<td>12</td>
</tr>
<tr>
<td>Colonoscopy every 10 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15</td>
</tr>
</tbody>
</table>
Benefits, Harms, and Burden of Colorectal Screening Strategies Over a Lifetime (4)

Harms: Lifetime No. of colonoscopies per 1000 individuals screened

<table>
<thead>
<tr>
<th>Screening Method and Frequency</th>
<th>Model Estimates, Complications per 1000 Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexible sigmoidoscopy every 5 y</td>
<td>Middle: 10, Low: 9, High: 12</td>
</tr>
<tr>
<td>FIT-DNA every 3 y</td>
<td>Middle: 9, Low: 9, High: 10</td>
</tr>
<tr>
<td>FIT every year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Middle: 10, Low: 10, High: 11</td>
</tr>
<tr>
<td>HSGFOBT every year</td>
<td>Middle: 11, Low: 11, High: 11</td>
</tr>
<tr>
<td>CT colonography every 5 y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Middle: 10, Low: 10, High: 11</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 10 y plus FIT every year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Middle: 11, Low: 11, High: 12</td>
</tr>
<tr>
<td>FIT-DNA every year</td>
<td>Middle: 12, Low: 12, High: 13</td>
</tr>
<tr>
<td>Colonoscopy every 10 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Middle: 15, Low: 14, High: 15</td>
</tr>
</tbody>
</table>

Complications per 1000 Screened
Benefits, Harms, and Burdens of Recommended Screening Strategies Over a Lifetime

B. Benefit: Colorectal Cancer Deaths Averted, per 1,000 Screened

- FIT 1y: 22 (20-23)
- gFOBT 1y: 22 (20-23)
- SIG 10y + FIT 1y: 23 (22-24)
- COL 10y: 24 (22-24)

C. Harms (Proxy): Lifetime Number of Colonoscopies, per 1,000 Screened

- FIT 1y: 1,757 (1,739-1,899)
- gFOBT 1y: 2,253 (2,230-2,287)
- SIG 10y + FIT 1y: 2,289 (2,248-2,490)
- COL 10y: 4,049 (4,007-4,101)

Source: CISNET, 2015

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Recommended Screening Tests
ACS and USPSTF

- Colonoscopy
- High Sensitivity Fecal Occult Blood Testing
  - High Sensitivity Guaiac Tests
  - Fecal Immunochemical Tests
- Flexible Sigmoidoscopy (FSIG)*
- CT colonography*
- Stool DNA*

*Highly limited utilization in US at present
Colonoscopy

• Allows direct visualization of entire colon lumen

• Screening, diagnostic and therapeutic

• 10 yr interval

• The most common screening test in US (>80%)
Influence of colonoscopic polypectomy on risk of death from colorectal cancer

Colonoscopic polypectomy was associated with a 53% reduction in colorectal cancer mortality.
Why Colonoscopy is NOT “a gold standard screening test”

- Evidence does not support “best test” or “gold standard”
  - Colonoscopy misses ~ 10% of significant lesions in expert settings
  - Wide variation in quality (when data are captured and available)
  - More costly on a one-time basis
  - Higher potential for patient injury than other tests
Quality Issues with Colonoscopy

- Poor pre-procedure documentation
- Poor prep
- Failure to reach the cecum
- Rapid withdrawal time
- Adverse events
- Over and under utilization of the procedure
- Highly variable reports
- Poor feedback
- Highly variable adenoma detection rate
- Interval cancers

- Most endoscopists are unaware of “their numbers,” since most facilities do not track their data.
Adenoma Detection Rate (ADR)

- ADR – rate of detection of adenomatous polyps at screening colonoscopy in population age 50+
- At least one adenoma should be found 30 percent of the time in men, and 20 percent of the time in women (25 percent composite)
- Studies indicate wide variation in ADR, even among clinicians in same practice
- ADR associated with adverse outcomes in a number of studies
Data from 314,872 colonoscopies performed between January 1, 1998 and December 31, 2010

136 gastroenterologists

To be included GI had to have completed > 300 colonoscopies and 75 or more screening examinations during the study period

ADRs ranged from 7.4% to 52.5%.

Corley et al. NEJM 2014: 370: 1298-1306
Hazard ratios for ADR and risk of advanced stage CRC, and fatal CRC

Advance Stage CRC

Fatal CRC
More Reasons Why Colonoscopy is NOT gold standard

- **Greater patient requirements** for successful completion
  - Requires a bowel prep and facility visit, and often a pre-procedure specialty office visit

- **Access**
  - Limited by insurance status, local resources

- **Patient preference**
  - *Many adults don’t want an invasive test or a test that requires a bowel prep*
Types of Stool Tests*

A) Tests that detect blood (Fecal Occult Blood Tests)
   - Two types
     - Guaiac-based FOBT**
     - Immunochemical (FIT) FOBT

B) Tests that detect aberrant DNA
   - One test (Cologuard) available in U.S. Cologuard is a multi-target CRC screening test
     - Combines DNA mutation test with FIT
     - Limited use at present

* Appropriate only for those at **average risk** for CRC
** Performance influenced by whether the test is performed at home or in the clinic
Advantages of Stool Tests

- Less expensive
- No bowel preparation.
- Done in privacy at home.
- No need for time off work or assistance getting home after the procedure.
- Non-invasive – no risk of pain, bleeding, perforation
- Limits need for colonoscopies – required only if stool blood testing is abnormal.
Guaiac Tests

- Most common type in U.S.
- Solid evidence (3 RCT’s)
- 30 year f/u (NEJM Oct 2013)
- Need specimens from 3 bowel movements
- Non-specific
- Results influenced by foods and medications
- Better sensitivity with newer versions (Hemoccult Sensa)
- Older forms (Hemoccult II) **not recommended**!
Single Panel FOBT Following Digital Rectal Exam

- Reasons to STOP single sample FOBT
  - Not recommended by the manufacturer of any test
  - Not recommended by any CRC screening guideline
  - Lowest sensitivity of any CRC screening test, i.e., less than 5% for advanced neoplasia
Fecal Immunochemical Tests (FIT)

- Specific for human blood and for lower GI bleeding
- Results not influenced by foods or medications
- Some types require only 1 or 2 stool specimens
- Higher sensitivity than older forms of guaiac-based FOBT
- Costs more than guaiac tests (but higher reimbursement)
Recommendations on Fecal Immunochemical Testing to Screen for Colorectal Neoplasia: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer

Douglas J. Robertson,¹,²,* Jeffrey K. Lee,³,* C. Richard Boland,⁴ Jason A. Dominitz,⁵ Francis M. Giardiello,⁶ David A. Johnson,⁷ Tonya Kaltenbach,⁸ David Lieberman,⁹ Theodore R. Levin,¹⁰ and Douglas K. Rex¹¹

This review has multiple purposes. First, to assist health care practitioners in the use of FIT, evidence is summarized about performance characteristics and the comparative effectiveness of FIT. Second, to assist practices or organizations developing FIT-based screening programs, evidence is summarized regarding its application (eg, number of tests and quantitative cut-off values for a positive test). Finally, additional sections of the review address important clinical questions regarding FIT. When possible, recommendations were made using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.¹⁴
Accuracy of Fecal Immunochemical Tests for Colorectal Cancer

Systematic Review and Meta-analysis

Jeffrey K. Lee, MD, MAS; Elizabeth G. Liles, MD, MCR; Stephen Bent, MD; Theodore R. Levin, MD; and Douglas A. Corley, MD, PhD

Background: Performance characteristics of fecal immunochemical tests (FITs) to screen for colorectal cancer (CRC) have been inconsistent.

Purpose: To synthesize data about the diagnostic accuracy of FITs for CRC and identify factors affecting its performance characteristics.

Data Sources: Online databases, including MEDLINE and EMBASE, and bibliographies of included studies from 1996 to 2013.

Study Selection: All studies evaluating the diagnostic accuracy of FITs for CRC in asymptomatic, average-risk adults.

Data Extraction: Two reviewers independently extracted data and critiqued study quality.

Data Synthesis: Nineteen eligible studies were included and meta-analyzed. The pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of FITs for CRC were 0.79 (95% CI, 0.69 to 0.86), 0.94 (CI, 0.92 to 0.95), 13.10 (CI, 10.49 to 16.35), 0.23 (CI, 0.15 to 0.33), respectively, with an overall diagnostic accuracy of 95% (CI, 93% to 97%). There was substantial heterogeneity between studies in both the pooled sensitivity and specificity estimates. Stratifying by cutoff value for a positive test result or removal of discontinued FIT brands resulted in homogeneous sensitivity estimates. Sensitivity for CRC improved with lower assay cutoff values for a positive test result (for example, 0.89 [CI, 0.80 to 0.95] at a cutoff value less than 20 μg/g vs. 0.70 [CI, 0.55 to 0.81] at cutoff values of 20 to 50 μg/g) but with a corresponding decrease in specificity. A single-sample FIT had similar sensitivity and specificity as several samples, independent of FIT brand.

Limitations: Only English-language articles were included. Lack of data prevented complete subgroup analyses by FIT brand.

Conclusion: Fecal immunochemical tests are moderately sensitive, are highly specific, and have high overall diagnostic accuracy for detecting CRC. Diagnostic performance of FITs depends on the cutoff value for a positive test result.

Primary Funding Source: National Institute of Diabetes and Digestive and Kidney Diseases and National Cancer Institute.


For author affiliations, see end of text.
Pooled sensitivity and specificity for FIT

79% sensitivity


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FIT Quality Issues

All FIT are not created equal

- FDA clears guaiac FOBTs and FITs only for “detection of blood” – no assessment of cancer detection capability is required
- Most FDA-cleared FITs have no published data on their performance for detection of CRC or adenoma
- Some tests are currently marketed as “single sample” tests with no performance data on this use
- FDA is updating clearance criteria
## FITs With Published Data*
Available in the US

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoccult-ICT/Flexsure OBT</td>
<td>Beckman-Coulter</td>
</tr>
<tr>
<td>Hemosure One Step</td>
<td>WHPM, Inc.</td>
</tr>
<tr>
<td>InSure / ColoVantage</td>
<td>Clinical Genomics</td>
</tr>
<tr>
<td>OC-Sensor / OC FIT-CHEK</td>
<td>Polymedco</td>
</tr>
<tr>
<td>OC-Auto Micro</td>
<td>Polymedco</td>
</tr>
<tr>
<td>OC-Light</td>
<td>Polymedco</td>
</tr>
</tbody>
</table>
PCP Perceptions of Screening Tests

- FOBT/FIT used, but:
  - Effectiveness questioned by many clinicians
  - Lack of knowledge re: performance of new vs. older forms of stool tests, other quality issues

- Colonoscopy viewed as the best screening test, but many patients face barriers or not willing
  - Often recommended despite access or other challenges
  - Focus on colonoscopy associated with low screening rates in a number of studies
  - Patient preferences rarely solicited
Many Patients Prefer FOBT

Randomized clinical trial in which 997 patients in the San Francisco PH care system received different recommendations for screening:

<table>
<thead>
<tr>
<th>Recommended Test</th>
<th>Completed Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>38%</td>
</tr>
<tr>
<td>FOBT</td>
<td>67%</td>
</tr>
<tr>
<td>Colonoscopy or FOBT</td>
<td>69%</td>
</tr>
</tbody>
</table>

Many patients will forgo screening if they are not offered an alternative to colonoscopy.

(Inadomi et al. 2012)
Many Patients Prefer FOBT/FIT

- Diverse sample of 323 adults given detailed side-by-side description of FOBT and colonoscopy (DeBourcy et al. 2007)
  - 53% preferred FOBT
  - Almost half felt very strongly about their preference

- 212 patients at 4 health centers rated different screening options with different attributes (Hawley et al. 2008)
  - 31% preferred FOBT
  - 37% preferred colonoscopy

- Nationally representative sample of 2068 VA patients given brief descriptions of each screening mode (Powell et al. 2009)
  - 29% preferred FOBT
  - 37% preferred colonoscopy
Making the Best Use of Scarce Resources: Screening colonoscopy vs. FIT

- Represents 20 patients

Screening colonoscopy (refer 1,000 patients)

- Eligible population, referred
- Patient refusal, no shows
- 1 cancer in 400-1000 colonoscopies

FIT testing (2,000 patients)

- Eligible population
- Patients with a positive FIT
- 1 cancer in 20 colonoscopies

Slide courtesy of Dr. G. Coronado

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Stool DNA Test (sDNA)

- Fecal occult blood tests detect blood in the stool – which is intermittent and non-specific
- Colon cells are shed continuously
- Polyps and cancer cells contain abnormal DNA
- Stool DNA tests look for abnormal DNA from cells that are passed in the stool*
Multi-Target Stool DNA Test

- One test currently available (Cologuard)
- Combines tests for stool DNA markers associated with cancers and adenomas plus FIT
Cologuard Sample Collection Kit

Cologuard Patient Guide. 2014.

Rx only. Complete product labeling available at CologuardTest.com

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Home Sample Collection Kit Steps

1. [Image 1]
2. [Image 2]
3. [Image 3]
4. [Image 4]
5. [Image 5]
6. [Image 6]

Rx only. Complete product labeling available at CologuardTest.com.
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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.
Cologuard

• FDA has cleared it for marketing as CRC screening test
  • Every 3 year testing interval approved by FDA
• CMS has agreed to cover Cologuard for *average risk* Medicare beneficiaries age 50 – 85 yrs
  • Medicare will reimburse ~ $500 q 3 yrs. for the test (price includes “navigation” component)
  • Private insurance coverage – limited
• All positive tests must be evaluated by colonoscopy
• Included in current ACS guideline
Cologuard

• No long term data on CRC outcomes
• No evidence for 3 year screening interval
• Concern that some DNA mutations associated with non-CRC cancers
  • Management of patients with positive Cologuard test and normal colonoscopy is uncertain
• Eligible for “no cost sharing” screening benefit – but like other stool tests, *if the test is positive, patients are subject to cost-sharing for follow up colonoscopy*
Radiographic CRC Screening Tests

Double Contrast Barium Enema

CT Colonography, aka Virtual Colonoscopy
CT Colonography

2-D View

3-D View

Colonoscopy View

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CTC to Screen for Colorectal Neoplasia in Asymptomatic Adults

Prospective multi-center DoD trial of 1,233 asymptomatic adults
CTC Screening for Colorectal Neoplasia in Asymptomatic Adults

Prospective multi-center DoD trial of 1,233 asymptomatic adults comparing tandem CT Colonography with Optical Colonoscopy

<table>
<thead>
<tr>
<th>Size Threshold:</th>
<th>≥ 6 mm</th>
<th>≥ 8 mm</th>
<th>≥ 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By-Patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC Sensitivity</td>
<td>88.7%</td>
<td>93.9%</td>
<td>93.8%</td>
</tr>
<tr>
<td>OC Sensitivity</td>
<td>92.3%</td>
<td>91.5%</td>
<td>87.5%</td>
</tr>
<tr>
<td>CTC Specificity</td>
<td>79.6%</td>
<td>92.2%</td>
<td>96.0%</td>
</tr>
</tbody>
</table>

Conclusion: CTC comparable to OC for detection of clinically relevant polyps

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Results: For all samples, sensitivity of Epi proColon for CRC detection was 73.3% (95% CI 63.9–80.9%) and 68.0% (95% CI 58.2–76.5%) FIT.

Specificity of the Epi proColon test was 81.5% (95% CI 75.5–86.3%) compared with 97.4% (95% CI 94.1–98.9%) for FIT.

When test results for Epi proColon and FIT were combined, CRC detection was 88.7% at a specificity of 78.8%.

Conclusions: At a sensitivity of 72%, the Epi proColon test is non-inferior to FIT for CRC detection, although at a lower specificity. With negative predictive values of 99.8%, both methods are identical in confirming the absence of CRC.
The Problem and a Path Ahead—A Key Element of the FDA application for epi proColon was addressing the non-adherence challenge

- **A third** of US men and women remain **unscreened**
  
  1 of 3 or ~ 35 million screening eligible women and men are not compliant with screening guidelines

- **Choice of options** increases participation
  
  Colonoscopy alone does not address the problem
  
  Additional options will enhance outcome

- **Blood-based** methods will expand the market
  
  Incremental market opportunity > $1 Bn per year
  
  Additional options will enhance outcome
Conclusion—What are the CRC Screening Challenges Today?

• This just in... *What happens to the Affordable Care Act?*

• Achieving 80% screening rate requires:
  • Effective reminder systems and effective informed decision making
  • Appropriate use of colonoscopy alternatives

• To spur growth, must educate PCPs on:
  • Evidence of FOBT/FIT efficacy
  • Stool test program quality features
  • Importance of exploring patient preferences and offering options
  • New and emerging test options

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Conclusion—What are the CRC Screening Challenges Today?

• Offering options: How many are too many?
• Access to colonoscopy for adults without insurance, or high deductible plans
  • Community-based Links of Care Models
  • Navigation
• Colonoscopy Quality Assurance Programs
  • Endoscopists must track the ADR, and preferably the multiple ADR
  • Measure quality on key indicators
  • Have a plan for corrective action

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