Colorectal Cancer

- The third most common cancer in U.S., and the third deadliest
  - More than 140,000 new cases each year
  - Close to 50,000 deaths nationwide

- More than 1.1 million Americans living with a current or past diagnosis of colorectal cancer
• Incidence and deaths rates have fallen steadily for the past 20 yrs

U.S. Colorectal Cancer Mortality 1975-2005

- Black Male
- White Male
- Black Female
- White Female
Trends

Research suggests that these declines are due in large part to:

- Screening and polyp removal, preventing progression of polyps to invasive cancers
- Screening → detecting cancers at earlier, more treatable stages
- CRC treatment advances
Colorectal Cancer Risk Factors

- **Age**
  - 90% of cases occur in people 50 and older

- **Gender**
  - slight male predominance, but common in both men and women

- **Race/Ethnicity**
  - African Americans have highest incidence and mortality rate of all groups in US, Hispanics the lowest (with considerable variation depending on country of origin)
  - Increased rates also documented in Alaska Natives, some American Indian tribes, and Ashkenazi Jews
*Increased risk with:*

- Personal history of inflammatory bowel disease, adenomatous polyps, or colon cancer
- Family history of adenomatous polyps, colon cancer, genetic syndromes and other conditions

*Individuals with these risk factors may require earlier and more intensive screening*
Colorectal Cancer

Sporadic (average risk) (65%–85%)

Family history (10%–30%)

Hereditary nonpolyposis colorectal cancer (HNPCC) (5%)

Familial adenomatous polyposis (FAP) (1%)

Rare syndromes (<0.1%)
Different types:

- **Hyperplastic**
  - minimal cancer potential
- **Adenomatous**
  - approximately 90% of colon and rectal cancers arise from adenomas
Normal to Adenoma to Carcinoma

Human colon carcinogenesis progresses by the dysplasia/adenoma to carcinoma pathway
Benefits of Screening

- **Cancer Prevention**
  - Removal of pre-cancerous polyps to prevent cancer (unique aspect of colon cancer screening)

- **Improved survival**
  - Early detection markedly improves chances of long-term survival
Benefits of Screening

Survival Rates by Disease Stage*

<table>
<thead>
<tr>
<th>Stage of Detection</th>
<th>5-yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>89.8%</td>
</tr>
<tr>
<td>Regional</td>
<td>67.7%</td>
</tr>
<tr>
<td>Distant</td>
<td>10.3%</td>
</tr>
</tbody>
</table>

*1996 - 2003
Colorectal Screening Rates

- Just 40% of colorectal cancers are detected at the earliest stage.
- A little more than half* of Americans over age 50 report having had a recent colorectal cancer screening test.
- Slow but steady improvement in these numbers over the past decade (but all are not benefiting to the same degree).

*varies based on data source
Percent of Adults Who Report a Recent CRC Screening Test, NHIS 2000 & 2005

Shift from FOBT & FSIG to Colonoscopy is Evident

- Fecal Occult blood test in the past year
- Flexible sigmoidoscopy in the past five years
- Colonoscopy in the past ten years
- Combined FOBT/Endoscopy
## Colorectal Cancer Screening Among Adults Aged 50 and Older, US, 2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% Fecal Occult Blood Test</th>
<th>% Sigmoidoscopy or Colonoscopy</th>
<th>% Combined Endoscopy/FOBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10.3</td>
<td>52.2</td>
<td>54.9</td>
</tr>
<tr>
<td>Women</td>
<td>9.7</td>
<td>48.6</td>
<td>52.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>9.1</td>
<td>45.7</td>
<td>49.1</td>
</tr>
<tr>
<td>65+</td>
<td>11.1</td>
<td>55.5</td>
<td>58.1</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (non-Hispanic)</td>
<td>10.3</td>
<td>52.7</td>
<td>56.0</td>
</tr>
<tr>
<td>African American (non-Hispanic)</td>
<td>8.9</td>
<td>47.3</td>
<td>48.9</td>
</tr>
<tr>
<td>Asian</td>
<td>12.1</td>
<td>42.6</td>
<td>47.8</td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>4.5</td>
<td>31.7</td>
<td>33.1</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>7.8</td>
<td>34.6</td>
<td>37.2</td>
</tr>
<tr>
<td>Education (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 or fewer</td>
<td>8.1</td>
<td>34.0</td>
<td>37.3</td>
</tr>
<tr>
<td>12</td>
<td>8.1</td>
<td>48.1</td>
<td>50.8</td>
</tr>
<tr>
<td>13 to 15</td>
<td>12.9</td>
<td>52.2</td>
<td>56.3</td>
</tr>
<tr>
<td>16 or more</td>
<td>10.8</td>
<td>61.9</td>
<td>64.5</td>
</tr>
<tr>
<td>Health Insurance Coverage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10.3</td>
<td>52.6</td>
<td>55.7</td>
</tr>
<tr>
<td>No</td>
<td>8.8</td>
<td>12.7</td>
<td>19.5</td>
</tr>
<tr>
<td>Immigration**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born in US</td>
<td>10.1</td>
<td>51.9</td>
<td>55.0</td>
</tr>
<tr>
<td>Born in US Territory</td>
<td>5.8</td>
<td>42.3</td>
<td>45.9</td>
</tr>
<tr>
<td>In US less than 10 years</td>
<td>8.0</td>
<td>22.5</td>
<td>28.0</td>
</tr>
<tr>
<td>In US 10 years or more</td>
<td>9.7</td>
<td>38.7</td>
<td>41.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10.0</strong></td>
<td><strong>50.2</strong></td>
<td><strong>53.2</strong></td>
</tr>
</tbody>
</table>
Colorectal Cancer Screening* (%) 
Adults 50 Years and Older by State, 2006-2008

*A fecal occult blood test within the past year or a sigmoidoscopy or colonoscopy within the past 10 years. These estimates do not distinguish between screening and diagnostic exams.
A flexible sigmoidoscopy or colonoscopy within the past five years. Note: Data from participating states and the District of Columbia were aggregated to represent the United States.

Trends in Recent* Fecal Occult Blood Test Prevalence (%), by Educational Attainment and Health Insurance Status, Adults 50 Years and Older, US, 1997-2004

*A fecal occult blood test within the past year. Note: Data from participating states and the District of Columbia were aggregated to represent the United States.

Colorectal Screening Rates Low: Reasons (according to Patients)

- Low awareness of CRC as a personal health threat
- Lack of knowledge of screening benefits
- Fear, embarrassment, discomfort
- Time
- Cost
- Access
- “My doctor never talked to me about it!”
The Current CRC Guidelines were a Joint Effort of 5 Organizations

- American Cancer Society

- US Multi-Society Task Force on Colorectal Cancer
  - American Gastroenterological Association
  - American College of Gastroenterology
  - American Society of Gastrointestinal Endoscopists

- American College of Radiology
CRC Screening Guidelines:

CRC screening tests are grouped into two categories:

- Tests that detect cancer and pre-cancerous polyps*
- Tests that primarily detect cancer

* It is the strong opinion of the consensus guidelines group that *colon cancer prevention* should be the primary goal of CRC screening.

- Exams that are designed to detect both early cancer and pre-cancerous polyps should be encouraged if resources are available and patients are willing to undergo an invasive test.
- If the full range of screening tests are not available, physicians should make every effort to offer at least one test from each category.
**CRC Screening Guidelines:**

- **Two new tests recommended:**
  - stool DNA (sDNA) and
  - computerized tomographic colonography (CTC) – sometimes referred to as virtual colonoscopy

- **The guidelines establish a sensitivity threshold for recommended tests**

- **The guidelines delineate important quality-related factors for each form of testing**

The full guideline and evidence article can be accessed at: [http://caonline.amcancersoc.org/cgi/content/full/CA.2007.0018v1](http://caonline.amcancersoc.org/cgi/content/full/CA.2007.0018v1)
ACS/USMSTF/ACR Screening Guidelines

Beginning at age 50, both men and women at average risk for developing colorectal cancer should use one of the screening tests below:

<table>
<thead>
<tr>
<th>Tests That Detect Adenomatous Polyps and Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexible sigmoidoscopy (FSIG) every 5 years*, or</td>
</tr>
<tr>
<td>Colonoscopy every 10 years, or</td>
</tr>
<tr>
<td>Double contrast barium enema (DCBE) every 5 years*, or</td>
</tr>
<tr>
<td>CT colonography (CTC) every 5 years*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tests That Primarily Detect Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual guaiac-based fecal occult blood test (gFOBT) with high test sensitivity for cancer *, ** or</td>
</tr>
<tr>
<td>Annual fecal immunochemical test (FIT) with high test sensitivity for cancer*, ** or</td>
</tr>
<tr>
<td>Stool DNA test (sDNA), with high sensitivity for cancer*, interval uncertain</td>
</tr>
</tbody>
</table>

* Colonoscopy should be done if test results are positive.
** For gFOBT or FIT used as a screening test, the take-home multiple sample method should be used. gFOBT or FIT done during a digital rectal exam in the doctor’s office is not adequate for screening.
Current CRC Guidelines Continue to Emphasize Options Because:

- Evidence does not yet support any single test as “best”
- Uptake of screening remains disappointingly low
- Individuals differ in their preferences for one test or another
- Primary care physicians differ in their ability to offer, explain, or refer patients to all options equally
- Access is uneven geographically, and in terms of test charges and insurance coverage
- Uncertainty exists about performance of different screening methods with regard to benefits, harms, and costs (especially on programmatic basis)
If tests that can prevent CRC are preferred, why not recommend them alone?

- Greater patient requirements for successful completion
  - Endoscopic and radiologic exams require a bowel prep and an office or facility visit

- No true “gold standard”
  - Colonoscopy misses 5 – 10% of significant lesions in expert settings

- Higher potential for patient injury than fecal testing
  - Risk levels vary between tests, facilities, and practitioners

- Patient preference
  - Many individuals don’t want an invasive test or a test that requires a bowel prep
  - Some prefer to have screening in the privacy of their home
  - Some may not have access to the invasive tests due to lack of coverage or local resources
Tests for Polyps and Cancer
Colonoscopy allows a doctor to directly see inside the entire bowel.
Colonoscopy

- Provides opportunity to find both cancer and polyps
- Growths can be biopsied and polyps can be completely removed
- Has become the most common test used for CRC screening in the US
Colonoscopy

Limitations

- Expense
- Limited access in some settings
- Logistics (time off work, need driver, etc.)
- Prep
- Complications (sedation, bleeding, perforation, etc.)
- Misses up to 10% of significant lesions
- Questions regarding impact on R colon
Flexible Sigmoidoscopy (FSIG)

- Similar to colonoscopy, but uses a shorter instrument
- FSIG allows doctor to directly see the lower one-third of the colon (an area where a high proportion of cancers are detected)
- Use has fallen precipitously over the past decade
Anatomy and CRC Distribution

- Transverse: 15%
- Descending: 5%
- Ascending: 25%
- Cecum: 25%
- Sigmoid: 25%
- Rectosigmoid: 10%
- Rectum: 20%
Double Contrast Barium Enema

- X-ray study using barium (white) and air (dark) in the colon to look for irregularities
- Use as a screening tool has fallen dramatically over the past decade
CT Colonography (CTC)

*AKA “Virtual Colonoscopy”

Images courtesy of Beth McFarland, MD
CT Colonography

Rationale

- Allows detailed evaluation of the entire colon
- A number of studies have demonstrated a high level of sensitivity for cancer and large polyps
- Minimally invasive (rectal tube for air insufflation)
- No sedation required
CT Colonography

2-D view

3-D view

Polyp

Polyp1

Polyp

Courtesy of Beth McFarland, MD
CTC Virtual “Fly Through”

Courtesy of Beth McFarland, MD
## CTC vs. Optical Colonoscopy: Meta-Analyses

<table>
<thead>
<tr>
<th>Polyp Size</th>
<th>CTC Performance</th>
<th>Pooled Sensitivity</th>
<th>Pooled Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10mm</td>
<td>85-93%</td>
<td>97%</td>
<td>86-93%</td>
</tr>
<tr>
<td>6-9 mm</td>
<td>70-86%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>85.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Halligan 2005, Mulhall 2005
The American College of Radiology Imaging Network (ACRIN) study is a multi-center study with each site using state of the art technology.

- 15 center trial
- 2,531 asymptomatic patients
  - Either 2D or 3D
  - Multiple manufacturers
- Almost all had colonoscopy
### ACRIN Results

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomas &gt; 1 cm</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>Polyps 6-9 mm</td>
<td>84%</td>
<td>86-89%</td>
</tr>
</tbody>
</table>
CT Colonography

Limitations

- Requires full bowel prep (which most patients find to be the most distressing part of colonoscopy)
- Colonoscopy is required if abnormalities are detected, sometimes necessitating a second bowel prep
- Steep learning curve for radiologists
- Limited availability to high quality exams in many parts of the country
- Most insurers do not currently cover CTC as a screening modality
CT Colonography

Limitations

- Extra-colonic findings can lead to additional testing (may have both positive and negative connotations)

- Questions regarding:
  - Significance of radiation exposure
  - Management of small polyps
Tests That Mainly Detect Cancer
Fecal Occult Blood Tests

Rationale

- Detect blood in the stool
- Cancers tend to bleed
- Large polyps also may bleed (although less likely to bleed than cancers)

Two methods:

- Guaiac
- Immunochemical (FIT)
Guaiac Tests

- Most common type in US
- Best evidence (3 RCT’s)
- Need specimens from 3 bowel movements
- Non-specific
- Results influenced by foods and medications
- Older forms (Hemoccult II) have unacceptably low sensitivity
- Better sensitivity with newer forms (Hemoccult Sensa)
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
- Slightly more costly than guaiac tests

FIT use in the US will likely increase due to recent elimination of guaiac-based testing by LabCorp and Quest Labs
Stool DNA Test (sDNA)

Rationale

- 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*

*All positive tests should be followed with colonoscopy
**Genetic Model of Colorectal Cancer**

- **Bat-26 (HNPCC)**
  - Mutations in APC, K-ras, and p53
  - Dwell Time: Many decades

- **Bat-26 (Sporadic)**
  - Mutations in APC, K-ras, and p53
  - Dwell Time: 2-5 years

Optimum phase for early detection

Courtesy of Barry M. Berger, MD, FCAP  EXACT Sciences
Collection bucket inserted into bracket and installed under toilet seat

Patient supplies whole stool sample; no diet or medication restrictions

Patient seals sample in outer container and freezer pack

Patient seals container and ships back to designated lab (all packing materials and labels supplied)
Stool DNA

Limitations

- Misses some cancers
- Sensitivity for adenomas with current commercial version of test is low
- Technology (and test versions) are in transition
- Costs much more than other forms of stool testing (approximately $300 - $400 per test)
- Not covered by most insurers
Stool DNA

Limitations (cont.)

- Appropriate re-screening interval is not known
- Not clear how to manage positive stool DNA test if colonoscopy is negative
- FDA issues
- Test availability
Quality Issues
Quality Issues in CRC Screening

- The medical literature reflects quality concerns related to essentially all forms of testing

- Examples include:
  - Inadequate flex sig insertion depth
  - Abbreviated colonoscopy withdrawal times
  - Poor sensitivity of in-office FOBT
## FOBT Sensitivity: Take Home vs. In-Office

### Sensitivity of Take Home vs. In-Office FOBT

<table>
<thead>
<tr>
<th>FOBT method</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Hemoccult II)</td>
<td></td>
</tr>
<tr>
<td>3 card, take-home</td>
<td>All Advanced Lesions</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>23.9 %</td>
</tr>
<tr>
<td></td>
<td>43.9 %</td>
</tr>
<tr>
<td>Single sample, in-office</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All Advanced Lesions</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>4.9 %</td>
</tr>
<tr>
<td></td>
<td>9.5 %</td>
</tr>
</tbody>
</table>

Collins et al, Annals of Int Med Jan 2005
Conclusion

- In-office FOBT is essentially **worthless** as a screening tool for CRC

However;

- In a recent national survey, nearly *a quarter* of physicians reported using single-sample, in-office FOBT as their primary method of screening for colorectal cancer.

Nadel et al, Jnl Gen Int Med Jan 2010
FOBT Quality Issues

**National Survey 1999-2000**

- In office only 32.5%
- Both 41.2%
- Home only 26.3%
- 75% using in office test in 2000

**Follow up study 2010 showed no improvement**

- In office only 24.9%
- Both 52.9%
- Home only 22.2%
- 75% still using in office test in 2010

Nearly 75% reported using single-sample, in-office FOBT as a primary method of screening – during BOTH timeframes

Guidelines recommend HOME Test

In-office single FOBT is **not recommended** as screening tool for CRC by any organization

Guidelines state that all positive FOBT’s should be evaluated with **colonoscopy**. However:

- **Follow up of abnormal test (2005)**
  - Repeat FOBT 29.7%

- **Follow up of abnormal test (2010)**
  - Repeat FOBT 17.8%

High Quality Stool Testing

- CRC screening by FOBT should be performed with *high-sensitivity* FOBT -- either FIT or a highly sensitive gFOBT (such as Hemoccult SENSA).
  - Older, less sensitive guaiac tests (such as Hemoccult II) should not be used for CRC screening.
- Tests should be repeated yearly
- In-office FOBT is essentially **worthless** as a screening tool for CRC and must be **strongly discouraged**.
- All positive screening tests should be evaluated by colonoscopy
Thank You!