Colorectal Cancer

- Second most common cancer in the United States
- Overall mortality rate approaches 60%
- Approximately 5% of the US population will develop CRC in their lifetime and half will die of the disease
- Estimated 145,290 new cases of CRC and 73,470 deaths in 2005
  - Massachusetts-3560 new cases and 1380 deaths

Number / 100,000 population

- **Incidence in men**
- **Incidence in women**
- **Mortality in men**
- **Mortality in women**

Age group (years) 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85+

Colorectal Cancer

- Average age of diagnosis in symptomatic patients is 67
- Five-year survival rate is 90 percent when CRC is detected in an early localized stage
- Only 1/3rd of patients with CRC are diagnosed in the earliest stage
- ~93% cases occur in persons $\geq$ age 50
Screening for Colorectal Cancer

• Screening: testing asymptomatic individuals for disease
  – sensitive, specific, affordable, acceptable to asymptomatic patients, and able to reduce mortality and morbidity

• Surveillance: interval testing in high risk patients

• Diagnosis: evaluation of patients with symptoms or with positive screening tests
Screening for Colorectal Cancer

- Substantial evidence exists to suggest that most, if not all, colorectal carcinomas arise from preexisting adenomas
- Time course from normal colonic mucosa to polyp and then to carcinoma probably requires 7-15 years
- Mortality rate for CRC declining over past 20 years
  - Combination of decreased incidence and advances in detection and treatment
Screening for Colorectal Cancer

- Suitable disease for screening
  - common malignancy with a long asymptomatic preclinical phase
  - high survival rate if detected in its early stage
- Good screening tests exist
  - Several options are available
  - Not screening is no longer an option
- Prevention of CRC should be achievable by identifying and removing adenomatous polyps from asymptomatic patients
Screening = Early Detection and Prevention

- Early detection of CRC → decreased mortality
- Prevention (removal of adenomatous polyp) → decreased incidence
CRC Awareness is Increasing

- Medicare Funding
- State laws mandating insurance
- “Couric Effect” – Today Show
- National awareness campaigns
- Endorsement by guideline groups
  - ACG, AGA, ACS, ASCRS, ACR, AAFP
  - US Preventive Services Task Force
Medicare Funding for CRC Screening

• Effective 1/1/98 for Medicare patients over 50
  – Annual FOBT for average risk patients
  – Screening FS every 4 years for average risk patients
  – Colonoscopy every two years for high risk individuals

• Effective 7/1/01 for Medicare patients over 50
  – Colonoscopy every 10 years for average risk patients
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Colon polyps. Stop them before they go bad.

Colon cancer almost always starts with a polyp. Get the polyp early and stop colon cancer before it even starts. And that’s for both men and women. Just get a test from your doctor. 1-800-ACS-2345 or cancer.org

Colon cancer. Get the test. Get the polyp. Get the cure.
CRC Awareness is Increasing

- Medicare Funding
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  - US Preventive Services Task Force
US Preventive Services Task Force

- Grade A Recommendation for colorectal cancer screening
- Optimal method of screening not clear
Cost-Effectiveness
(Cost/Year Life Saved)

- Mandatory motorcycle helmets $2,000
- Colorectal cancer screening $25,000
- Breast cancer screening $35,000
- Dual airbags in cars $120,000
- Smoke detectors in homes $210,000
- School bus seat belts $1,800,000

CRC screening may in fact be cost saving
Average Risk Asymptomatic Patients Starting at Age 50

- Annual FOBT
- Flexible Sigmoidoscopy every 5 years
- FOBT and Flexible Sigmoidoscopy
- DCBE every 5-10 years
- Colonoscopy every 10 years
Average-Risk Options Are Not Equivalent

- Effectiveness
- Up front costs
- Risk
- Acceptability
Fecal Occult Blood Test
Fecal Occult Blood Test

Pros:
- Proven effective in randomized trials
- Non-invasive
- Cost-effective

Cons:
- Mortality reduction low (15-33%)
- Compliance with annual testing unlikely in community practice
- Evaluation of positive tests often inadequate

Flexible Sigmoidoscopy

**Pros**
- Easier prep
- Performed by PCPs
- Inexpensive
- No Sedation

**Cons**
- Prep often limits insertion
- Miss rates higher
- Reduced willingness to repeat
- Does not examine right colon

Levin et al Gastro 2002;123:1786
Loeve et al JNCI 2000;92:557
Anatomic distribution of colorectal cancers and polyps according to the reach of the sigmoidoscope or colonoscope

Proximal colonic lesions (beyond reach of the sigmoidoscope)
36% of cancers
34% of Adenomatous polyps

Distal colorectal lesions (within reach of the sigmoidoscope)
64% of cancers
66% of Adenomatous polyps
Sigmoidoscopy to Detect Advanced Colonic Pathology

- **Half Full**
  - Sigmoid exam detects 68-80% of all patients with advanced neoplasia

- **Half Empty**
  - Sigmoid exam fails to detect 52-62% of all patients with advanced proximal neoplasia
Screening Colonoscopy

• One of the most powerful tools in clinical medicine
• Polypectomy plus surveillance colonoscopy reduced incidence of CRC by 76-90% (NPS)
• Surveillance accounts for 20-40% of the costs for CRC
  – 90% of the benefit comes from index colonoscopy
  – Efforts must be made to decrease number of surveillance examinations
Colonoscopy

Pro's
- Most sensitive
- Long lasting protection
- Single session diagnosis and therapy
- Comfortable

Con's
- Perceived as invasive
- Highest risk
- Requires bowel preparation
- Imperfect sensitivity

Rex, Am J Gastroenterol 2000;95:868
Colonoscopy – It’s Not Perfect

- Inherent miss rate
- Flat and depressed lesions
- Variable Growth Rates
  (e.g., microsatellite instability)

Rex, Am J Gastroenterol 2001;95:952
### Complications of Screening Tests

#### Complication Rates

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>(Perforation/Hemorrhage)</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barium enema</td>
<td>1/10,000</td>
<td>&lt; 1/10,000</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>1-2/10,000</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>10-30/10,000</td>
<td>1-3/10,000</td>
</tr>
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</table>
## CRC Screening Options

### Detection Rates

<table>
<thead>
<tr>
<th></th>
<th>Cancers</th>
<th>Polyps ≥ 1 cm</th>
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<tbody>
<tr>
<td>FOBT</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Flex Sig</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>FOBT + FS</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>DCBE</td>
<td>85%</td>
<td>50%</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>95%</td>
<td>95%</td>
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</table>
## CRC Screening Recommendations

<table>
<thead>
<tr>
<th></th>
<th>FOBT</th>
<th>FS</th>
<th>FS +FOBT</th>
<th>Colon</th>
<th>DCBE</th>
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</thead>
<tbody>
<tr>
<td><strong>USPSTF</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td><strong>GI Consortium</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>ACSG</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>ACG</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Preferred</td>
<td>+</td>
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<tr>
<td><strong>Canadian Task Force</strong></td>
<td>+</td>
<td>+</td>
<td>Insufficient</td>
<td>Insufficient</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
Do Something

- All persons aged 50 years and older should begin regular screening
- High-risk individuals may need to begin screening earlier
- Less than half the eligible population has had any screening
- Choice of which test is less important than initiating some screening
The Future for CRC Screening

- Virtual colonoscopy (CT Colography)
- Stool analysis for DNA mutations
CT Colography

• Novel imaging technique in which helical computed tomography (CT) is used to generate 2D and 3D displays of the colon and rectum
Advantages: CT Colography

- Minimally invasive, no sedation required
- Retrograde and antegrade viewing
- Ability to traverse strictures
- Accurate anatomic localization of tumors
3D Trial: CT Colography

- Multicenter – military hospitals
- 1233 asymptomatic patients

<table>
<thead>
<tr>
<th></th>
<th>10mm</th>
<th>8mm</th>
<th>6mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Sens AD by pt</td>
<td>94%</td>
<td>94%</td>
<td>89%</td>
</tr>
<tr>
<td>CC Sens AD by pt</td>
<td>88%</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>CT Specificity</td>
<td>96%</td>
<td>92%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Pickhardt, NEJM 2003; 349: 2191
Disadvantages: CT Colography

- Performance in an average risk population highly variable
- Stringent bowel prep required
- Uncomfortable
- Flat lesions not seen
- Colonoscopy needed to confirm and biopsy
- Not endorsed by authoritative groups
- Not covered by Medicare or third-party payers
Indications 2005: CT Colography

- Incomplete colonoscopy
  - Screening
  - Obstructing tumor or stricture
- Evaluation of high-risk symptomatic patients
- Pre-operative tumor localization and staging
- CRC screening for patients who refuse colonoscopy
CT Colography for CRC Screening

• Under optimal conditions, virtual colonoscopy compares favorably with conventional colonoscopy for detecting clinically significant lesions

• Definition of “significant” lesion based on polyp size (?6 mm vs. 10 mm) remains highly controversial

• Marked site-to-site variation in performance precludes widespread endorsement by authoritative groups

• Not covered by Medicare or third-party payers
**Rationale: Stool-Based DNA Testing**

- CRC results from an accumulation of alterations in known tumor suppressor genes *(APC, p53)* and proto-oncogenes *(K-ras)*
- CRC cells with mutated DNA continuously shed into the feces
- DNA is stable in stool
Fecal DNA Testing

- 5 targets K-RAS, P53, APC, BAT-26, long DNA
- Sensitivity for cancer 52%
- Sensitivity of FOBT for cancer 13%
- Sensitivity for advanced adenomas 18%
- Specificity 94%

Advantages: Stool-Based DNA Testing

- “Total colon” examination
- Non-invasive, safe
- No bowel preparation
- Convenient (single sample collected at home)
- Rapidly improving technology
Stool-Based DNA Testing: PreGen-Plus™

- Assay system developed by EXACT Sciences
- 23 genetic markers assayed:
  - > 21 point mutations in K-ras, APC, p53
  - > 1 microsatellite instability marker = Bat-26
  - > “Long DNA” (> 200 Bp)
- Single whole stool (≥ 30 gm) required
- Specific for human DNA
Multitarget Stool-Based DNA Testing
Summary of Published Literature

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>~70%</td>
<td>95%</td>
</tr>
<tr>
<td>Adenomas (≥ 1cm)</td>
<td>≥ 50%</td>
<td>95%</td>
</tr>
</tbody>
</table>
Prospective, Multicenter Trial Comparing Stool-Based DNA vs. FOBT*

*Sensitivity

<table>
<thead>
<tr>
<th></th>
<th>Cancer</th>
<th>Advanced Adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB-DNA</td>
<td>52%</td>
<td>15%</td>
</tr>
<tr>
<td>FOBT</td>
<td>13%</td>
<td>11%</td>
</tr>
</tbody>
</table>

* n = 5400 average-risk subjects; 31 cancers

Disadvantages: Stool-Based DNA Testing

- Limited sensitivity (especially for advanced adenomas)
- Optimal interval not defined
- High cost ($600-800)
- Not endorsed by authoritative groups
Recommended Screening Strategies 2005

Beginning at age 50: Average Risk

• Annual FOBT
• Flexible sigmoidoscopy (FS) every 5 years
• Annual FOBT plus FS every 5 years
• Annual FOBT plus FS every 5 years
• Colonoscopy every 10 years
Recommended Screening Strategies 200?

*Beginning at age 50: Average Risk*

- Annual FOBT
- Flexible sigmoidoscopy (FS) every 5 years
- Annual FOBT plus FS every 5 years
- Annual FOBT plus FS every 5 years
- Colonoscopy every 10 years
- Virtual colonoscopy every 5 years
- Stool based DNA testing every 3-5 years
Colorectal Cancer Screening

• Compelling rationale

• Suitable tests

• Favorable cost-effectiveness