Colorectal cancer screening
A puzzle of tests and strategies

A. Van Gossum, MD, PhD

Head of the Clinic of Intestinal Diseases and Nutritional Support
Department of Gastroenterology
Hôpital Erasme – ULB - Brussels

December 4, 2010
CRC screening

- Colorectal cancer affects both men and women
- 2\textsuperscript{nd} biggest cancer killer in UK (> 16,000 deaths in 2008)
- Almost 20\% of cases present as on emergency
- Survival \sim 50\%
- 75\% of cases have non known risk factors
- No feasible means of primary prevention
- Very costly to diagnose and treat
  - NHS spends > £ 1 billion/year on diagnosis and treatment of CRC in England

Cunningham D, Lancet 2010
10 years

1000 → 100 → 25
Number of new cases diagnosed and age-specific rates per 100,000 population, colorectal cancer, by sex, UK 2000

Meza R, Cancer Res 2010
Figure 1. Death rates from CRC per 100,000 population.\textsuperscript{1}

Figure 2. CRC incidence rates per 100,000 and rates of CRC screening in individuals older than age 50.\textsuperscript{1}
Decrease in colorectal cancer incidence

- Screening?
- Other factors:
  - hormone-replacement (menopause)
  - use of low dose aspirin
  - use of NSAIDS
CRC screening

Invite all eligible at risk

All men and women aged 50+

Not opportunistic
CRC screening

<table>
<thead>
<tr>
<th></th>
<th>Population</th>
<th>Opportunistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invitation</td>
<td>active</td>
<td>passive</td>
</tr>
<tr>
<td>Screening method</td>
<td>fixed</td>
<td>variable</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Specificity</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Benefits maximised</td>
<td>population</td>
<td>individual</td>
</tr>
<tr>
<td>Harms minimised</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

Miles et al; A perspective from countries using organised screening programs, Cancer 2004; 101: 1201-13
## Risk for CRC

<table>
<thead>
<tr>
<th>Average</th>
<th>Moderate</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All individuals</td>
<td>Personal/familial history of polyp/adenoC</td>
<td>HNPCC</td>
</tr>
<tr>
<td>&gt; 50 y</td>
<td>IBD (Crohn/UC)</td>
<td>FAP</td>
</tr>
<tr>
<td></td>
<td>Acromegaly</td>
<td>Peutz-Jeghers</td>
</tr>
<tr>
<td></td>
<td>Ureterosigmoidostomy</td>
<td>Juvenile polyposis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MUTYH-associated polyposis</td>
</tr>
</tbody>
</table>

Cairns S, GUT 2010
Tools for CRC screening in average risk population

- Fecal screening tests
- Flexible sigmoidoscopy
- Colonoscopy
- CT colonography (CTC)
- Capsule endoscopy
CRC screening tools

Fecal screening test

Fecal occult blood test (FOBT)  Stool-DNA tests

Standard GAIAC-FOBT (g-FOBT [Hemocult®])  Immunological test I-FIP
CRS screening test
Gaiac g-FOBT

- Detects peroxidase activity of heme
- Not specific for human blood
- False ☨: red meat or peroxidase-containing foods
- False Θ: vitamin C
- 2 or 3 stool samples (separate days) > one sample
- Sensitivity for advanced neoplasia: 25-30%
- If positive test → risk of cancer: 3 – 4 x ↑
Gaiac-FOBT

• At home
• Low cost
• Effectiveness:
  – repeat annual testing if test negative
  – completion of colonoscopy if test positive
• Levels of adherence: uncertain
CRC screening
Fecal immunological test

- Antibodies specific to human hemoglobin, albumin or other blood components
- Less prone to false positives
- Sensitivity higher than gaiac-FOBT
- One sample = 2 or 3 samples
- Higher adherence

van Rossum LG, Int J Cancer 2010
SENS: 50%; SPEC: 95-98%; VPP: 40%

The proof is in the numbers

87% Sensitivity for colorectal cancer
In a clinical trial of 240 people, InSure™ FIT was shown to have 87% sensitivity for cancer.²

98% Specificity for significant neoplasia
InSure FIT provides accurate screening with less worry about false positives.²

InSure FIT detects blood with greater sensitivity
**CRC screening**

**Fecal screening test**

- May detect early stage tumors
- Multiple fecal test $\rightarrow$ reduced mortality
- Modest reduction on incidence of CRC
- Must be repeated (bi)annually
- Low adherence for repeating
- Completion to colonoscopy if \( \oplus \)

*Hol L, Eur J Cancer 2010*
*Grazzini G, GUT 2010*
CRC screening
Structural tests
Flexible Sigmidoscopy
CRC screening
Structural tests
Sigmoidoscopy

Advantages
• easier prep
• no sedation
• low discomfort
• performed by physicians or nurses (UK)

Disadvantages
• no polypectomy
• no detection of proximal lesions (30% - more common in women and older > 60 y)
• need for subsequent total colonoscopy
CRC screening
Structural tests
Flexi-sigmoidoscopy

Effect on incidence and mortality debatable

Norway (7 years follow-up) NO

UK* (12 years follow-up) YES

*Atkin W, Lancet 2010
CRC screening
Structural tests
colonoscopy
CRC screening
Structural tests
Colonoscopy

Advantages
- complete exam
- ability to remove polyp

Disadvantages
- colon prep
- sedation/anesthesia
- one-day off
- risk of complications (perforation/bleeding)
- false Θ
CRC screening
Structural tests
Colonoscopy

- Indirect clinical evidence to support efficacy and accuracy:
  - reduction in CRC incidence: 53 – 72%
  - reduction in CRC mortality: 31%
  - no reduction in mortality for proximal colon cancer

Lieberman D, Gastro 2010
Wallace M, Gastro 2010
CRC screening
Structural tests
Colonoscopy

• Missed lesions:
  – 2 – 12% of polyps larger than 10 mm
  – more than 20% of polyps larger than 6 mm

• Flat lesions:
  – need for improving detection and characterization
CRC screening

- Risk of developing advanced neoplasia within 5 years after a negative colonoscopy is low: 1.4 – 2.4%

- Incidence rate of interval cancer within 3-5 years after removal of adenomas is 0.3 – 0.9%
CRC screening test
Colonoscopy
Performance indicators

• Bowel prep quality
• Completeness of exam
• Time of procedure (withdrawal time > 6 mm)
• Cecal intubation rate
• Adenoma detection rate
• Appropriate follow-up
• Polyp retrieval rate
• Unplanned or adverse events
• Appropriate follow-up recommendations
• Patient satisfaction

Kaminski M, NEJM 2010
POLYPOID

FLAT

DEPRESSED/ULCERATED

Paris’ classification

[Images of different types of lesions]
Villous content

High grade dysplasia

Advanced adenomas

# adenomas ≥ 3

Adenoma > 1cm
Coloscopy with chromoendoscopy
CRC screening
Structural tests
CT colonography
CRC screening test

Structural tests

CTC

• CTC > barium enema
• CTC = colonoscopy for detecting polyp ≥ 10 mm
• CTC:
  – 90% of polyps ≥ 10 mm (14% false-positive)
  – 65% of polyp 6-9 mm
  – not reported for < 6 mm
CRC screening
Structural tests
CTC

Advantages
• less invasive than colonoscopy
• no sedation
• low risk of perforation

Disadvantages
• radiation exposure
• complete bowel prep \(\rightarrow\) if \(\oplus\) \(\rightarrow\) 2nd colon prep
• extracolonic structures
• polyp < 6 mm not detected or reported
CRC screening test

Structural tests

CTC

Current recommendation: 1 or more polyps 6 mm or larger

→ colonoscopy

= 15-25% of patients

Mergener K, GE Clin North Am 2010
CRC screening test

Structural tests

CTC

• Polyp < 5 mm
• Likelihood of advanced histology 1-7%
• If 3 or more adenomas:
  – higher risk for developing advanced adenoma
PillCam COLON Capsule 1

- 2-sided video cameras:
  - 4 images per second
  - 2 images per second per camera

- Dimensions:
  - Diameter: Same as PillCam SB
  - Length: 5 mm longer than PillCam SB

- Automatic light control and optics optimized for colon visualization

- ~10 hours operating time
Multi-center European Study

Capsule Endoscopy Versus Colonoscopy for the Detection of Polyps and Cancer*

A. Van Gossum¹, M. Munoz Navas², I. Fernandez-Urien², C. Carretero², G. Gay⁴, M. Delvaux⁴, M.G. Lapalus³, T. Ponchon³, H. Neuhaus⁵, M. Philipper⁵, G. Costamagna⁶, M.E. Riccioni⁶, C. Spada⁶, L. Petruzziello⁶, C. Fraser⁷, A. Postgate⁷, A. Fitzpatrick⁷, F. Hagenmuller⁸, M. Keuchel⁸, N. Schoofs¹, J. Devière¹

Brussels¹, Pamplona², Lyon³, Nancy⁴, Düsseldorf⁵, Roma⁶, London⁷, Hamburg⁸

* New England J of Medicine 361;13, July 16, 2009
Patients

- 332 patients enrolled
- 320 patients included in the accuracy analysis;
  - 144 (45%) females and 176 (55%) males
  - 58.5 years mean age (22-84 range)
- Indications and age group:

<table>
<thead>
<tr>
<th></th>
<th>22-49 years</th>
<th>50-84 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients known to have colonic disease</td>
<td>55</td>
<td>57</td>
<td>112 (35%)</td>
</tr>
<tr>
<td>Patients suspected of having colonic disease</td>
<td>7</td>
<td>201</td>
<td>208 (65%)</td>
</tr>
</tbody>
</table>

- 64 (19%)  
- 264 (81%)  
- 320
Location of PillCam Post Ingestion

At 10:00 hours

92.8% excreted

0.3%

0.3%

1.6% proximal to colon

4.7%

92.8% excreted
Lesion prevalence and Detection Accuracy
PillCam vs. Colonoscopy
Per Patient Data (n=320)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Colonoscopy Prevalence(^1)</th>
<th>PillCam Sensitivity</th>
<th>PillCam Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyp</td>
<td>87 (27%)</td>
<td>64%</td>
<td>84%</td>
</tr>
<tr>
<td>Adenoma</td>
<td>71 (22%)</td>
<td>68%</td>
<td>82%</td>
</tr>
<tr>
<td>Advanced adenoma(^2)</td>
<td>49 (15%)</td>
<td>73%</td>
<td>79%</td>
</tr>
</tbody>
</table>

\(^1\) No. of patients (% of patients)

\(^2\) Vilous features and high grade dysplasia
Effect of Cleansing on Detection Accuracy
**PillCam vs. Colonoscopy**
**Per Patient Data**

<table>
<thead>
<tr>
<th>Lesion ≥ 6mm</th>
<th>Colonoscopy Prevalence&lt;sup&gt;1&lt;/sup&gt;</th>
<th>PillCam Sensitivity</th>
<th>PillCam Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyp</td>
<td>87 (27%)</td>
<td>64%</td>
<td>84%</td>
</tr>
<tr>
<td>Advanced adenoma&lt;sup&gt;2&lt;/sup&gt;</td>
<td>49 (15%)</td>
<td>73%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>59 (18%)</td>
<td>75%</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>33 (10%)</td>
<td>88%</td>
<td>78%</td>
</tr>
</tbody>
</table>

<sup>1</sup> No. of patients (% of patients)

<sup>2</sup> Vilous features and high grade dysplasia
Colon Lesions

- ≥ 10mm
- Ascending colon

- <6 mm
- Rectum
Angle of view: 172 degrees
4 to 35 frames/second
Polyp size estimation tool
Guidelines of ACS – MSTF - ACR

Stool-blood tests

Structural colon tests
(Flexi, colonoscopy, barium enema, CTC)

Cancer

Early cancer
Cancer precursor lesions

ACS = American Cancer Society
MSTF = Multi-Society Task Force
ACR = American College of Radiology

Levin B et al, Gastroenterology 2008
<table>
<thead>
<tr>
<th>Test</th>
<th>ACS/MSTF/ACR</th>
<th>USPSTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoccult II</td>
<td>Not recommended</td>
<td>Annually</td>
</tr>
<tr>
<td>HS-FOBT/FIT</td>
<td>Annually</td>
<td>Annually</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>Every 5 years</td>
<td>Every 5 years (suboptimal)</td>
</tr>
<tr>
<td>FOBT and sigmoidoscopy</td>
<td>Annually and every 5 years</td>
<td>Mid-interval and every 5 years</td>
</tr>
<tr>
<td>DCBE</td>
<td>Every 5 years</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Fecal DNA</td>
<td>Yes; interval not specified</td>
<td>No recommendation for or against owing to insufficient evidence</td>
</tr>
<tr>
<td>CTC</td>
<td>Every 5 years</td>
<td>No recommendation for or against owing to insufficient evidence</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Every 10 years</td>
<td>Every 10 years</td>
</tr>
<tr>
<td>Overall</td>
<td>Structural test preferable; prevention better than early detection</td>
<td>Any test acceptable</td>
</tr>
</tbody>
</table>

CTC, computed tomographic colonography; DCBE, double-contrast barium enema; FOBT, fecal occult blood test; HS-FOBT/FIT, high-sensitivity fecal occult blood test or fecal immunochemical test.
CRC screening
Cost-effectiveness

- Efficacy
- Surveillance strategies
- Adherence
- cost inputs

⇒ FOBT (< $ 40,000 per life-year saved)
  FOBT + FS (> $ 60,000 per life-year saved)
<table>
<thead>
<tr>
<th>Findings at baseline colonoscopy examination\textsuperscript{a}</th>
<th>Recommended interval for colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyps</td>
<td>10 y</td>
</tr>
<tr>
<td>Hyperplastic polyps: rectum-sigmoid</td>
<td>10 y</td>
</tr>
<tr>
<td>1–2 tubular adenomas (&lt;10) mm</td>
<td>5–10 y</td>
</tr>
<tr>
<td>3 or more tubular adenomas</td>
<td>3 y</td>
</tr>
<tr>
<td>Tubular adenoma (\geq10) mm</td>
<td>3 y</td>
</tr>
<tr>
<td>Adenoma with villous histology</td>
<td>3 y</td>
</tr>
<tr>
<td>Adenoma with high-grade dysplasia</td>
<td>3 y</td>
</tr>
<tr>
<td>Invasive cancer\textsuperscript{b}</td>
<td>1 y</td>
</tr>
<tr>
<td>Incomplete removal of neoplastic lesion</td>
<td>3 mo</td>
</tr>
</tbody>
</table>

Adapted from Winawer et al\textsuperscript{35} and Rex et al.\textsuperscript{90}
CRC screening
Number of life-years gained per 1,000 is similar for:

• Annual FIT
• Annual Hemoccult SENSA
• Colonoscopy at 10 y-year interval
• Hemoccult/3 y + Flexisigmoide/5 y
Screening issues

• Ideal screening technology:
  ➔ serum tests → identification specific genomic or proteomic patterns

• Women: log time of about 7 – 8 y
  (50 y-old male = 58 y-old female)

• Race:
  US: higher incidence and mortality for Blacks
Screening issues
When to stop screening?

After age 75 → benefit is reduced

After age 85 → risks might outweigh benefits but life-expectancy is increasing!
CRC screening

Rules for recommendations

1. Sensitivity of 50%
   “test sensitivity” versus “program sensitivity”

2. Primary goal
   colon cancer prevention
   (structural tests) > early detection
   (FOBT)
Conclusion
CRC screening

• Trend for a decline in the incidence and mortality of CRC in Western countries

Possible role of screening

• Distinguishing tests likely to detect early cancer (FOBT) from those that may detect early precursors of cancer

• All CRC programs have some advantages and limitations

• Adherence to the program and quality control of performance are mandatory