Screening for colorectal cancer

Antoni Castells, MD, PhD
Gastroenterology Department
Hospital Clínica, Barcelona
(castells@clinic.cat)
Screening in average-risk population: colonoscopy
Endoscopic polypectomy: CRC mortality

Zauber et al. NEJM 2012

↓Δ 47%
“In order to maximize the impact of the intervention and ensure high coverage and equity of access, only organized screening programs should be implemented, as opposed to case-finding or opportunistic screening”
Limitations of colonoscopy in population-based CRC screening

**Effective**
- Highest sensitivity and specificity
- No RCT demonstrating its efficacy
- Prevalence of advanced neoplasms: 10.2%\(^1\)

**Efficient**
- Huge economical effort:
  - Average-risk population (50-74 years-old) in the EU\(^2\): 146 million people
  - Costs (colonoscopy, 250 €): 3,650 M€ annually

**Harmless**
- Serious GI events (bleeding, perforation): 2.4‰\(^3\) → 35,040 patients per year

\(^1\)Quintero & Castells, *et al.* NEJM 2012
\(^2\)EUROSTAT
\(^3\)Warren *et al.* Ann Intern Med 2009
How to select those individuals who may benefit the most from colonoscopy?

Risk stratification based on:
- Individual characteristics
- Genetic/genomic profiling
- Use of “less invasive” methods
CRC screening in average-risk population

- No
  - Personal and/or familial risk factors
  - Age
    - < 50 years: No screen
    - ≥ 50 years: Annual or biennial FOBT and/or sigmoidoscopy / 5 years, or colonoscopy / 10 years

- U.S. Preventive Services Task Force
- U.S. Multi-Society Task Force on Colorectal Cancer
- American Cancer Society
- AEG – semFYC – Cochrane Guidelines
Screening in average-risk population: fecal occult blood testing (FOBT)

Evidence: 1a
Recommendation: A

1Mandel et al. NEJM 1993
2Hardcastle et al. Lancet 1996
3Kronborg et al. Lancet 1996

CRC mortality reduction

<table>
<thead>
<tr>
<th>Location</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minnesota (1)</td>
<td>-30%</td>
</tr>
<tr>
<td>Nottingham (2)</td>
<td>-15%</td>
</tr>
<tr>
<td>Funen (3)</td>
<td>-18%</td>
</tr>
</tbody>
</table>
### Guaiac-based FOBT vs. Fecal immunochemical testing (FIT)

<table>
<thead>
<tr>
<th></th>
<th>Guaiac (Hemoccult II®)</th>
<th>FIT (OC-Sensor®)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invited population</td>
<td>10,301</td>
<td>10,322</td>
<td></td>
</tr>
<tr>
<td>Stool samples</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Participation –no. (%)</td>
<td>4,836 (47%)</td>
<td>6,157 (60%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Test positivity</td>
<td>2.4%</td>
<td>5.5%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Adv. adenomas –no. (%)</td>
<td>46 (0.4%)</td>
<td>121 (1.1%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CRC –no. (%)</td>
<td>11 (0.1%)</td>
<td>24 (0.2%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Van Rossum et al. Gastroenterology 2008
Screening in average-risk population: flexible sigmoidoscopy

Colorectal cancer incidence

Colorectal cancer mortality

Evidence: 1b
Recommendation: A

Atkin et al. Lancet 2010
Screening in average-risk population: flexible sigmoidoscopy

<table>
<thead>
<tr>
<th>Distal lesion</th>
<th>No polyp</th>
<th>Hyperplastic</th>
<th>Adenoma</th>
<th>Advanced adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal advanced adenoma prevalence (%)</td>
<td>1.5</td>
<td>4.0</td>
<td>7.1</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Lieberman et al. NEJM 2000
Imperiale et al. NEJM 2000
### Criteria for colonoscopy referral

<table>
<thead>
<tr>
<th>Distal lesion characteristics</th>
<th>UK</th>
<th>SCORE (Italy)</th>
<th>NORCCAP (Norway)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma size</td>
<td>≥ 10 mm</td>
<td>&gt; 5 mm</td>
<td>Any</td>
</tr>
<tr>
<td>No. adenomas</td>
<td>≥ 3</td>
<td>≥ 3</td>
<td>Any</td>
</tr>
<tr>
<td>Villous histology</td>
<td>🟢</td>
<td>🟢</td>
<td>🟢</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>🟢</td>
<td>🟢</td>
<td>🟢</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>🟢</td>
<td>🟢</td>
<td>🟢</td>
</tr>
</tbody>
</table>
Individuals referred for colonoscopy according to each set of criteria

Sigmoidoscopy simulation in 5,059 individuals screened by colonoscopy (ColonPrev study)

Castells & Bessa et al. J Natl Cancer Inst 2013
Overall advanced neoplasm detection rate of simulated sigmoidoscopy

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>SCORE</th>
<th>NORCCAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. (%)</td>
<td>317 (6.3%)</td>
<td>340 (6.7%)</td>
<td>355 (7.0%)</td>
</tr>
<tr>
<td>OR (95% CI)*</td>
<td>0.57 (0.49-0.67)</td>
<td>0.62 (0.54-0.72)</td>
<td>0.65 (0.56-0.75)</td>
</tr>
<tr>
<td>P value*</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*With respect to colonoscopy, adjusted by age, gender and participating center

520 (10.3%) individuals with advanced neoplasm

Castells & Bessa et al. J Natl Cancer Inst 2013
Screening in average-risk population: colonoscopy

Meta-analysis of 6 observational studies
*(per protocol analysis)*

<table>
<thead>
<tr>
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<th>RR (95%CI)</th>
</tr>
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<tbody>
<tr>
<td>CRC incidence</td>
<td>0.31 (0.12 - 0.77)</td>
</tr>
<tr>
<td>CRC mortality</td>
<td>0.32 (0.23 - 0.43)</td>
</tr>
</tbody>
</table>

Evidence: 2b
Recommendation: B

Brenner *et al.* BMJ 2014
RCT on colonoscopy-based screening

- **NordICC study:**
  - Colonoscopy vs. usual care
  - Norway, Poland, The Netherlands, and Sweden

- **ColonPrev Study:**
  - Colonoscopy vs. biennial FIT
  - Spain

- **CONFIRM study:**
  - Colonoscopy vs. annual FIT
  - US (Veterans Administration)
ColonPrev study: hypothesis

- **Fecal immunochemical testing (FIT):**
  - Better sensitivity and specificity than gFOBT
  - Less effective but potentially better accepted than colonoscopy
  - Higher acceptance may counteract its lower efficacy in a population-based approach

FIT-based screening should not be inferior to colonoscopy-based strategies in terms of CRC-related mortality in average-risk individuals.
ColonPrev study: aims

Primary end-point

- To compare the efficacy of one-time colonoscopy vs. biennial FIT for the reduction of CRC-related mortality at 10 years in average-risk population

Secondary end-points

- Participation (1st round) and adherence (at 10 years) rates
- Diagnostic rate and yield (1st round and cumulative at 10 years) of advanced colorectal neoplasia
- Complication rate (1st round and cumulative at 10 years)
- Cost-efficacy
- Quality
ColonPrev study: design

Multicenter, randomized controlled trial in 8 Spanish regions and 15 participating centers

ClinicalTrials.gov number: NCT00906997
ColonPrev study: methodology (I)

Inclusion criteria
- Men and women aged 50-69 years

Exclusion criteria
- Personal history of CRC, colorectal adenoma or colorectal polyposis
- Personal history of inflammatory bowel disease
- Family history of colorectal polyposis, Lynch syndrome or familial CRC (≥2 FDR with CRC, or 1 FDR with CRC diagnosed <60 years of age)
- Severe comorbidity
- Previous total colectomy
- Not signed informed consent to participate
Exclusion criteria (temporary)

- Previous colorectal examination:
  - Colonoscopy or flexible sigmoidoscopy within 5 years
  - FOBT within 2 years
- Presence of colorectal symptoms (rectal bleeding, abdominal pain, changes in intestinal habits, weight loss, fatigue, etc.)
ColonPrev study: methodology (III)

- Cross-over between study groups is allowed
- Incomplete colonoscopy: CT-colonography
- Quality-assurance program:
  - Colonoscopy (i.e. bowel cleansing)
  - Recruitment process
- Online database (www.coloncrib.org)
- Communication plan
- Analysis by:
  - Intention-to-screen
  - As-screened
  - Per protocol
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ColonPrev study: flowchart

Eligible population (grouped by address)

Randomization 1:1

Information + invitation ± reminding letters

Appointment: Local Screening Office (questionnaire, post-randomization consent)

Group I: Biennial FIT (n= 27,749)

Group II: Colonoscopy (n= 27,749)
ColonPrev study: chronogram

- **Inclusion period (1st round)**: June 2009
- **FIT** (2011)
- **Analysis of participation and detection rate** *(NEJM 2012)*
- **2021**
- **End of 3rd round**
- **Screening (continued)**
- **Analysis of mortality**
- **Analysis of CRC incidence**
- **Cost-efficacy**
Participation and cross-over rates (intention-to-screen analysis)

**Participation rate**
- Colonoscopy: 24.60%
- FIT: 34.20%

**Cross-over rate**
- Colonoscopy > FIT: 6.20%
- FIT > colonoscopy: 0.40%

**OR, 0.63 (95% CI, 0.60-0.65)**

**OR, 16.8; 95% CI, 13.9-20.2)**

Diagnostic yield (intention-to-screen analysis)

FIT Colonoscopy

Cancer
30 (0.1%)
33 (0.1%)

Advanced adenoma
514 (1.9%)
231 (0.9%)

Non-advanced adenoma
1109 (4.2%)
119 (0.4%)

OR (adjusted by age, gender and participating center)

Colorectal cancer staging (as-screened analysis)

Stage I: 24
Stage II: 6
Stage III: 6

p=0.52

Colonoscopy: red
FIT: blue
Number needed to screen (per protocol analysis)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Colonoscopy</th>
<th>FIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>191</td>
<td>281</td>
</tr>
<tr>
<td>Advanced neoplasia</td>
<td>10</td>
<td>36</td>
</tr>
</tbody>
</table>
Number needed to scope (per protocol analysis)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Colonoscopy</th>
<th>FIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>191</td>
<td>18</td>
</tr>
<tr>
<td>Advanced neoplasia</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

Bar chart showing the number of individuals needed to scope for colonoscopy and FIT tests.
Limitations of current strategies

- **Invasiveness**: colonoscopy, sigmoidoscopy
- **Low sensitivity**: FOBT/FIT, sigmoidoscopy
- **Compliance**:
  - 55% in FIT-based screening (Barcelona’s CRC Screening Program)
  - <30% in colonoscopy-based screening (ColonPrev Study)
- **Coverage**:
  - 20% of eligible Spanish population
  - <60% of eligible US population (Shapiro et al. CEBP 2008)
Screening in a population-based scenario

Screening success = test sensitivity x compliance x accessibility
Ideal features of a screening test for CRC

- Highly sensitive
  - Early CRC stages
  - Precursor lesions
  - Right and left neoplasms
- Highly specific (↓false positive)
- Non-invasive
- User friendly
- No bowel preparation
- No diet restriction
- Affordable
- Widely distributable
The analysis of molecular markers representing the genetic and epigenetic alterations associated with CRC is an attractive strategy.

Exfoliation of neoplastic cells in the feces is a continuum process in patients with colorectal neoplasia.

Tumor cells and tumor markers also enter into the blood in patients with colorectal neoplasia.

Multi-target stool DNA test

Methylation markers
(NDRG4 and BMP3)

Mutation markers
(KRAS)

Fecal hemoglobin
(Exact-FIT, purpose designed)

Analytic Algorithm

11 biomarkers
2 multiplex DNA assays
1 FIT ELISA assay

Single test result: positive, negative

Positive: refer to colonoscopy

[+ Beta-Actin for total DNA content and normalization]
Fecal DNA testing (DeeP-C study)

A. Colorectal Cancer According to Stage

- Stage I: N=29, Sensitivity: 90%, P=0.04
- Stage II: N=21, Sensitivity: 95%, P=0.06
- Stage III: N=10, Sensitivity: 80%
- Stage IV: N=4, Sensitivity: 75%
- Stage I–III: N=60, Sensitivity: 90%, P=0.002

B. Cancer and Advanced Precancerous Lesions According to Location

- Proximal Cancer: N=30, Sensitivity: 90%, P=0.04
- Distal Cancer: N=35, Sensitivity: 80%
- Proximal Advanced Lesions: N=431, Sensitivity: 70%
- Distal Advanced Precancerous Lesions: N=325, Sensitivity: 60%, P<0.001

Imperiale et al. NEJM 2014
Methylated SEPT9 in plasma

- PRESEPT study: multicenter US and German study (Epigenomics)
- Aim: estimate the ability of mSEPT9 to detect invasive CRC in asymptomatic average-risk individuals
- Subjects ≥50 year-old scheduled for colonoscopy (32 centers)
- 1st generation commercially available assay (Epi proColon Assay®)

- 7,491 patients enrolled (1516 selected for analysis)
  - Invasive CRC: 53
  - Advanced adenoma: 315
  - Non-advanced adenomas: 210
  - Normal colonoscopy: 938
- Post-hoc analysis with three replicates

Church et al. Gut 2013
mSEPT9 in plasma (PRESEPT study)

Sensitivity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>35</td>
</tr>
<tr>
<td>Stage II</td>
<td>63</td>
</tr>
<tr>
<td>Stage III</td>
<td>46</td>
</tr>
<tr>
<td>Stage IV</td>
<td>77.4</td>
</tr>
<tr>
<td>All stages</td>
<td>63.9</td>
</tr>
</tbody>
</table>

Specificity

- Advanced adenoma: 11.2%
- Specificity: 91.4%

Church et al. Gut 2013
miRNAs: new family of biomarkers

- miRNAs are short RNA molecules (19-25 nt in length), regulating gene expression by inhibiting translation and/or triggering degradation of their target mRNA.

- miRNAs play important roles in a wide array of normal biological and cellular processes.

- miRNAs are involved in the pathogenesis of multiple cancers, including CRC:
  - OncomiRs
  - Tumor suppressor miRs

- Human microRNAs (mirBase v19.0): >2000

Nature Genetics 2004
Circulating miRNAs in CRC

- miRNAs expression profiling in plasma (21 CRC, 20 adenoma, 20 healthy subjects)
- Validation with qPCR in 135 subjects

miR-19a + miR-19b + miR-15b

Table 2. Predictability of the Best Plasma miRNA Signatures in Patients With CRC From Set 2

<table>
<thead>
<tr>
<th>Signatures</th>
<th>All CRC (n = 42)</th>
<th>TNM I/II (n = 21)</th>
<th>TNM III/IV (n = 21)</th>
<th>Right-sided (n = 14)</th>
<th>Left-sided (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (95% CI)</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>AUC (95% CI)</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>miR19a+</td>
<td>0.82 (0.73–0.90)</td>
<td>78.57</td>
<td>77.36</td>
<td>0.81 (0.71–0.92)</td>
<td>85.71</td>
</tr>
<tr>
<td>miR19b</td>
<td>0.84 (0.76–0.92)</td>
<td>78.57</td>
<td>79.25</td>
<td>0.81 (0.70–0.92)</td>
<td>76.19</td>
</tr>
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Giráldez et al. Clin Gastroenterol Hepatol 2013
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<td></td>
<td></td>
</tr>
<tr>
<td>TNM I/II (n = 21)</td>
<td>0.85 (0.75–0.96)</td>
<td>0.87 (0.71–0.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>71.43</td>
<td>80.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>92.45</td>
<td>79.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNM III/IV (n = 21)</td>
<td>0.81 (0.71–0.92)</td>
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<td></td>
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<td>Sensitivity</td>
<td>85.71</td>
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Giráldez et al. Clin Gastroenterol Hepatol 2013
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Giráldez et al. Clin Gastroenterol Hepatol 2013
Colonoscopy is the most accurate method for CRC screening, but its usefulness may be limited in a population-based scenario.

Fecal immunochemical testing and flexible sigmoidoscopy are adequate approaches for an organized screening program.

Evaluation of effectiveness of both FIT- and colonoscopy-based screening in terms of CRC mortality reduction should wait the results of ongoing RCTs.

Biomarker-based screening strategies may improve CRC prevention: new generation stool DNA testing seems to offer high performance, and blood-based tests promise better compliance.
“The best test is the one that gets done.”

Sidney Winawer, MD
Screening for colorectal cancer

Antoni Castells, MD, PhD
Gastroenterology Department
Hospital Clínic, Barcelona
(castells@clinic.cat)