The choice of methods for Colorectal Cancer Screening;

The Dutch experience

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The Netherlands
Colorectal cancer

- CRC 2nd cause of cancer related death
- >12,500 new patients each year in The Netherlands
- 5 years mortality rate 40-45%
- 2015; 14,000 new CRC patients
Population based CRC screening?

Screening and surveillance criteria Wilson en Jungner;

1. The disease is an important health problem
2. The burden of the disease and the number of patients that die of the disease is substantial
3. There are precursor lesions (adenoma)
4. Early detection increases prognosis
Choice of methods of CRC screening

- Test features
- Uptake
- Risks and burden
- Capacity
- Costs
- .......
Screening methods

- Fecal tests
  - Chemical FOBT
  - Immunochemical FOBT
  - DNA

- Endoscopy
  - Sigmoidoscopy
  - Colonoscopy

- CT-colonography
Screening methods; FOBT

**Guaiac FOBT (gFOBT)**
2 fecal samples of 3 different stools

\[
guaiac + H_2O_2 \quad \text{Oxidation} \quad \text{Colour change}
\]

Catalysed by heme

**Immunochemical FOBT (IFOBT)**
1 fecal sample

Fecal Hb + Latex anti-HbA \(\rightarrow\) Antigen-antibody complex
Screening methods; FOBT

Positive FOBT  →  Colonoscopy
Efficacy of FOBT

Several large and longterm RCT show a mortality reduction between 14-18 % with guaiac FOBT

However; Low sensitivity for CRC;

Chemical test (gFOBT);  11-37%
Immunochemical test (iFOBT);  66-75%
Screening methods; endoscopy

**Sigmoidoscopy**
- Anatomic extend: flexura hepatica
- Preparation: phosphate enema
- Sedation: rare

**Colonoscopy**
- Anatomic extend: cecum
- Preparation: 2-4L polyethylene glycol
- Sedation: often

![Diagram of colon and sigmoidoscope](image-url)
Sigmoidoscopy / colonoscopy

Positive test
1. Colorectal cancer
2. Advanced adenoma
3. $\geq 3$ adenomas

Positive sigmoidoscopy $\rightarrow$ colonoscopy
**Efficacy of sigmoidoscopy screening**

**Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial**

Wendy S Atkin, UK Flexible Sigmoidoscopy Trial Investigators

170 432 individuals randomized (1:2) into sigmoidoscopy or control group. FU 11 jr

**ITT:** 23% ↓ CRC incidence (HR 0.77 (0.70-0.84) in sigmo group

31% ↓ CRC related mortality (HR 0.69 (0.59-0.82) in sigmo group

Atkin et al. Lancet 2010;375:1624
Efficacy of sigmoidoscopy screening

PP: 33% ↓ CRC incidence (HR 0.67 (0.60-0.76) in sigmo group

43% ↓ CRC related mortality (HR 0.57 (0.45- 0.72) in sigmo group
Efficacy of colonoscopy unknown

No data about the effect of colonoscopy screening

The expectation is that the incidence of CRC and the CRC related mortality will further decrease (around 70-90%)
Potential drawbacks of endoscopy screening

• Low uptake
• Complications
• Burden
• Capacity
• Costs
CT colography

- Detection of large adenoma and CRC
- Less burdensome than endoscopy?
- Positive test: Colonoscopy
- Limited data about uptake, adverse events, costs
Results of Dutch screening trials
Dutch CRC screening trials

November 2006 – 2013

> 30,000 asymptomatic persons 50-75 yr

1; Dutch FOBT trial Amsterdam/Nijmegen & Rotterdam (CORERO); FOBT/ Sigmoidoscopy

2; Rotterdam & Amsterdam (COCOS); colonoscopie/ CT

AIM; uptake and feasibility
Results 1\textsuperscript{st} round FOBT and Sigmo

Highest uptake with immunochemical FOBT, > 60%
# Results 1st round FOBT and Sigmo

<table>
<thead>
<tr>
<th>Test</th>
<th>% Uptake</th>
<th>% Positive test</th>
<th>% True positives*</th>
<th>True positives per 1000 invited</th>
</tr>
</thead>
<tbody>
<tr>
<td>gFOBT</td>
<td>49</td>
<td>2.8</td>
<td>45</td>
<td>6</td>
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<tr>
<td>iFOBT&lt;sup&gt;50&lt;/sup&gt;</td>
<td>62</td>
<td>8.1</td>
<td>42</td>
<td>21</td>
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<tr>
<td>Sigmoidoscopy</td>
<td>32</td>
<td>10.2</td>
<td>100</td>
<td>33</td>
</tr>
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</table>

* of those with positive test

Hol, Gut 2010
Results 1st round iFOBT; positivity rate at different cut-offs

Hol, Gut 2010; Hol, Br J of Cancer 2009
Results 1\textsuperscript{st} round iFOBT; yield

![Bar graph showing results of 1\textsuperscript{st} round iFOBT yield.](image)

- **gFOBT**
  - Adv. adenoom: 0.9
  - CRC: 0.2

- **50ng**
  - Adv. adenoom: 2.5
  - CRC: 0.5

- **75ng**
  - Adv. adenoom: 2.2
  - CRC: 0.3

- **100ng**
  - Adv. adenoom: 2.0
  - CRC: 0.2

- **125ng**
  - Adv. adenoom: 1.8
  - CRC: 0.2

- **150ng**
  - Adv. adenoom: 1.6
  - CRC: 0.2

References:
- Hol, Gut 2010; Hol, British Journal of Cancer 2009
# Results 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} round iFOBT

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<tr>
<td>2\textsuperscript{nd} round</td>
<td>63</td>
<td>5.8</td>
<td>46</td>
<td>17</td>
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<tr>
<td>3\textsuperscript{rd} round</td>
<td>65</td>
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* of those with positive test

Van Rhoon, Gut 2012
Cost-effectiveness analysis of iFOBT
iFOBT with limited coloscopy capacity

Wilschut, JNCI 2011
Results COCOS trial (colo vs CT); uptake

Invitees
n = 8842

Colonoscopy
n = 5923

Participants
n = 1273 (22%)

CT colonography
n = 2919

Participants
n = 983 (34%)

P = <0.001

Stoop, Lancet Oncology 2012
Results COCOS trial; diagnostic yield per 100 participants

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<th>Colonoscopy</th>
<th>CTC</th>
<th>P-value</th>
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<td>Advanced adenomas</td>
<td>8.1</td>
<td>5.6</td>
<td>0.04</td>
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<td>Carcinoma</td>
<td>0.5</td>
<td>0.2</td>
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Results COCOS trial; diagnostic yield \textit{per 100 invitees}

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<td>1.9</td>
<td>0.67</td>
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<td>Carcinoma</td>
<td>0.1</td>
<td>0.2</td>
<td>0.55</td>
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Stoop, Lancet Oncology 2012
Conclusions Dutch trials

• Highest uptake with immunochemical FOBT, > 60%
• FIT cut-off can be altered based on coloscopy capacity
• Good uptake during repeated invitations
• Uptake for sigmoidoscopy, colonoscopy, CTC low

Hol, Gut 2010; Wilschut, Gastroenterology 2011; Wilschut, JNCI 2011; van Roon, Gut 2012; de Goede Gut 2012
Overall conclusions

1. CRC is an important health care problem

2. A well organized population based screenings program will reduce CRC burden and mortality

3. Based on simplicity, acceptance, test features and safety, the Dutch government has chosen the iFOBT to be the optimal screening method for the Netherlands.
Introduction of a population based CRC screening program for people 55 years of age and older
Dutch CRC screening program with iFOBT

- Automated, quantitative test
- Variable cut-off (50, 75, 100 ng/ml)
- Do it at home test
- One sample
- Thin test, fits in an envelop
- No dietary restrictions
Dutch CRC screening program with iFOBT

- All individuals 55-75 years of age
- Biannual
- Invitation & iFOBT by postage, including return envelop
- Cut-off 75 ng/ml
Dutch CRC screening program with iFOBT
Dutch CRC screening program with iFOBT
Dutch CRC screening program; ICT
Enrollment in steps
2013

New King

Introduction of our CRC screening program!!