Design issues

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Agenda

Population – setting

Comparator

Design issues

Prospective evaluation
Population - Setting

Average risk subjects targeted for screening population based setting
**FIT** New standard: improved sensitivity for CRC and better capacity to detect (advanced) adenomas

*repeated testing improves detection*

**Sigmoidoscopy:** comparator for the detection of pre-invasive lesions

Test offered at long intervals / once in the lifetime
New tests

New biomarkers: non invasive – blood or stool based tests repeated testing

New imaging methods
TC colonography, colon capsule endoscopy long interval

Capsule endoscopies will be trialled in England
Zosia Kmietowicz
Screening as a process/strategy

Performance as a result of

Test characteristics + positivity threshold + interval
Screening as a process/strategy

New test: Cut-off needs to be flexible

Performance should be measured simulating different cut-off levels, focusing on the positivity range of established population based programs.

The demand for endoscopy resources represents one of the main determinants of the sustainability of a program.

FIT: positivity threshold ideally low, in studies with colonoscopy follow-up only for subjects testing positive at either test to allow simulating comparisons for different cut-off levels.

![Graph showing direct comparison of sensitivity and specificity for advanced neoplasm of 9 quantitative FITs](Gastroenterology)
Test evaluation framework

Diagnostic Accuracy

Measured against a reference standard

Cross sectional design

Clinical utility

Effectiveness and harms over the spectrum of disease

Prospective design

The study sample should be representative of the population where the test is intended to be used
**Test evaluation framework**

**Preliminary assessment of the test characteristics is needed**

Technical refinement of the test

Analytical validity

Test reproducibility

**Early assessment of the diagnostic accuracy of the test in the population where it is intended to be used may be justified to address spectrum bias**

Stage distribution and possibly biological characteristics are different among SD CRCs as compared to clinically diagnosed CRCs

Predictive role of biomarkers might be different

Cases and controls should ideally be recruited in a screening population
Test evaluation framework

**Paired testing within ongoing screening programs**

- assessment of all those testing positive with the comparator test
- all (or a sub-sample of) those testing positive to the new-test only referred for assessment immediately

Case control studies nested within screening cohorts
Outcomes related to the impact on patients and on the health care system

Characteristics of population enroled in ongoing screening programs may influence the results

- non screening naïve population
- possible association of screening history and response to different tests
CRC detection rate

Stage distribution of SD CRCs at first and at subsequent screening

Detection of early stage lesions is a goal, but screening may increase the detection of indolent lesions

Change in the absolute risk of late stage diagnosis versus stage shift

Table 1. Comparison of Four Fecal Occult-Blood Tests in 8104 People.

<table>
<thead>
<tr>
<th>TEST AND FINDING</th>
<th>NEOPLASMS DETECTED no.</th>
<th>TRUE POSITIVE TEST no. of patients (%)</th>
<th>FALSE POSITIVE TEST no.</th>
<th>TRUE NEGATIVE TEST no. of patients (%)</th>
<th>FALSE NEGATIVE TEST no. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoccult II (8065 screened, 198 [2.5%] positive)</td>
<td></td>
<td></td>
<td></td>
<td>7845 (97.3)</td>
<td>22 (0.3)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>35</td>
<td>13 (0.2)</td>
<td>185 (2.3)</td>
<td>152 (1.9)</td>
<td>74 (0.9)</td>
</tr>
<tr>
<td>Polyp &gt;1 cm</td>
<td>107</td>
<td>33 (0.4)</td>
<td>152 (1.9)</td>
<td>7771 (96.8)</td>
<td>96 (1.2)</td>
</tr>
<tr>
<td>Combined</td>
<td>142</td>
<td>46 (0.6)</td>
<td>152 (1.9)</td>
<td>7771 (96.4)</td>
<td></td>
</tr>
<tr>
<td>Hemoccult II Sensa (7904 screened, 1073 [13.6%] positive)</td>
<td></td>
<td></td>
<td></td>
<td>6824 (86.3)</td>
<td>10 (0.1)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>34</td>
<td>27 (0.3)</td>
<td>1046 (13.2)</td>
<td>6791 (85.9)</td>
<td>40 (0.5)</td>
</tr>
<tr>
<td>Polyp &gt;1 cm</td>
<td>165</td>
<td>72 (0.9)</td>
<td>974 (12.3)</td>
<td>6791 (85.9)</td>
<td>33 (0.4)</td>
</tr>
<tr>
<td>Combined</td>
<td>129</td>
<td>99 (1.2)</td>
<td>974 (12.3)</td>
<td>6791 (85.9)</td>
<td></td>
</tr>
<tr>
<td>HemeSelect (7493 screened, 440 [5.9%] positive)</td>
<td></td>
<td></td>
<td></td>
<td>7043 (94.0)</td>
<td>10 (0.1)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>32</td>
<td>22 (0.3)</td>
<td>418 (5.6)</td>
<td>7009 (93.9)</td>
<td>34 (0.5)</td>
</tr>
<tr>
<td>Polyp &gt;1 cm</td>
<td>102</td>
<td>68 (0.9)</td>
<td>350 (4.7)</td>
<td>7009 (93.5)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>134</td>
<td>90 (1.2)</td>
<td>350 (4.7)</td>
<td>7009 (93.5)</td>
<td></td>
</tr>
<tr>
<td>Combination (Hemoccult II Sensa and HemeSelect) (7847 screened, 233 [3.0%] positive)</td>
<td></td>
<td></td>
<td></td>
<td>7603 (96.9)</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>32</td>
<td>21 (0.3)</td>
<td>212 (2.7)</td>
<td>7552 (96.6)</td>
<td>51 (0.7)</td>
</tr>
<tr>
<td>Polyp &gt;1 cm</td>
<td>102</td>
<td>51 (0.7)</td>
<td>161 (2.1)</td>
<td>7552 (96.6)</td>
<td>62 (0.8)</td>
</tr>
<tr>
<td>Combined</td>
<td>134</td>
<td>72 (0.9)</td>
<td>161 (2.1)</td>
<td>7552 (96.6)</td>
<td></td>
</tr>
</tbody>
</table>

*For carcinoma the percentages are based on the number of patients screened. For polyps the percentages are based on the number of patients screened minus the number with carcinoma detected in polyps.

Interval CRCs

Allison J et al. NEJM 1996
Prospective evaluation

Performance over repeated rounds

Programme sensitivity (cumulative DR with FIT)

Primary colonoscopy screening (Italy – subjects 50–69 years old):
CRC 0.8%; advanced adenoma 6.0%

Prospective program evaluation

Learning programs: ongoing programs as a platform for research / introducing new technologies


Biobanking within existing programs
Thank you for your attention