Design of trials going forward

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No conflict of interest to declare
Setting

Average risk subjects targeted for screening

population based setting

Performance as a result of

Test characteristics + positivity threshold + interval
Blood Based Screening

Colorectal Cancer

Multi Cancer
Preliminary assessment of the test characteristics is needed

New tests must meet established laboratory standards

Analytical validity

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 cancers as compared to clinically diagnosed cancers

Predictive role of biomarkers might be different

Cases and controls should ideally be recruited in a screening population
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
Comparator test

**FIT** New standard: improved sensitivity for CRC and better capacity to detect (advanced) adenomas

repeated testing improves detection

**Sigmoidoscopy:** comparator for tests aimed to detect pre-invasive lesions
Test offered at long intervals / once in the lifetime
Screening as a process/strategy

New test: Cut-off needs to be flexible

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

performance should be measured simulating different cut-off levels, focusing on the positivity range of established population based programs
**Test evaluation framework**

**Paired testing within ongoing screening programs**

All subjects are performing both the standard and the new test immediate TC assessment of

- all subjects who are positive on the comparator test
- all (or a sub-sample of) those testing positive with the new-test only

<table>
<thead>
<tr>
<th>3. Initial screening evaluations, single screen</th>
<th>Characteristics of disease detected are defined and false-referral rate identified. Acceptability, workloads.</th>
<th>Testing in a typical screening environment in separate cohorts. Include intention-to-screen analyses. N=600 (assessing participation rates) or N=10,000 (assessing relative performance)</th>
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</thead>
</table>
Outcome of interest: CRC detection

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.

A more favourable stage distribution, or a reduction in the absolute risk of late stage diagnosis, may be expected among subjects with previous negative exams, if the test can detect lesions at higher risk of progression.

Interval CRCs

<table>
<thead>
<tr>
<th>Table 1. Comparison of Four Fecal Occult-Blood Tests in 8104 People.</th>
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<tbody>
<tr>
<td><strong>TEST AND FINDING</strong></td>
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<tr>
<td>Hemocult II (8065 screened, 198 [2.5%] positive)</td>
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<tr>
<td>Carcinoma</td>
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<tr>
<td>Polyp ≥1 cm</td>
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<tr>
<td>Combined</td>
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<tr>
<td>Hemocult II Sensa (7904 screened, 1073 [13.6%] positive)</td>
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<tr>
<td>Carcinoma</td>
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<tr>
<td>Polyp ≥1 cm</td>
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<tr>
<td>Combined</td>
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<tr>
<td>HemeSelect (7493 screened, 440 [5.9%] positive)</td>
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<tr>
<td>Carcinoma</td>
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<tr>
<td>Polyp ≥1 cm</td>
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<tr>
<td>Combined</td>
</tr>
<tr>
<td>Combination (Hemocult II Sensa and HemeSelect)</td>
</tr>
<tr>
<td>(7847 screened, 233 [3.0%] positive)</td>
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</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 on colonoscopy.

Prospective evaluation

Colorectal Cancer

Allison J et al. NEJM 1996
Two main scenarios

The test detects cancers for which a validated screening test is available

Standard Of Care (SOC) screening

The test detects cancers for which no proven screening test is available
Comparative evaluation pan cancer test – SOC screening

Cross-sectional design to compare diagnostic accuracy - Paired testing

Phased evaluation approach as described for the evaluation of new CRC screening tests
Comparative evaluation
pan cancer test – SOC screening

Additional aims

Assessing the potential increase in population coverage when offering blood test to non responders to SOC screening

Pan cancer test as a triage test?

Example: orient management of screen detected lung nodules at spiral CT screening
Pan cancer test – no validated screening test available

Pan cancer test detects cancers for which no validated screening test is available

we cannot be certain that the DETECT-A blood test used in our study helped any patient

(Lennon AM et al Science 2020)

Phased approach not applicable

RCT having mortality as end-point
Men / women
Target age range for CRC, breast and lung cancer screening

SOC + blood test

Management based on SOC screening tests results

SOC + blood test

PET-CT + SOC + additional diagnostic assessments

intermediate outcomes: stage distribution of cancers detected in the blood test group and in the usual care group
Pan cancer test – no validated screening test available

Open issues

Target population

Average risk versus high-risk subjects

Screening interval

Screening interval for blood tests needs to be defined

Integrating SOC screening
Test evaluation

Organized screening programs represent an ideal platform to implement comparative effectiveness research. The framework of learning screening programs, adopting a randomized design to assess the effectiveness of changes within ongoing established programs might facilitate the comparative assessment of new technologies.

(Longitudinal samples repositories, integrated with risk factor data, may accelerate the development of new cancer screening technologies.)

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Thank you for your attention

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