Colorectal Cancer Screening in Average-Risk Population: a Pragmatic, Multicenter, Randomized Controlled Trial Comparing Colonoscopy and Immunochemical Fecal Occult Blood Testing

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WEO Colorectal Cancer Screening Committee Screening Colonoscopy Trials Workgroup DDW 2018 Workshop
Hypothesis

✓ Fecal immunochemical testing (FIT):
  - Better sensitivity and specificity than gFOBT.
  - Less effective but better accepted than colonoscopy.
  - Higher acceptance may counteract its lower efficacy.

FIT screening would be noninferior to colonoscopy screening with respect to a reduction in mortality related to CRC among average-risk individuals.
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

1) **At baseline screening (1st round):** participation rate, diagnostic yield, major complications and consume of resources

2) **At completion of the trial (2021):** accumulative participation and compliance rates, diagnostic yield, major complications, consume of resources and cost-effectiveness
Study design

• Conducted in 8 Spanish regions

- Without population-based program
- With population-based program
Study groups

- **Group I**: biennial FIT (OC Sensor®) in one stool sample, followed by colonoscopy when a positive result (cut-off, 15 µg Hb/g of feces)

- **Group II**: one-time colonoscopy

*Testing was free of charge for all participants*
Methodology (I)

Inclusion criteria

- Asymptomatic men and women aged 50-69 years.

Exclusion criteria (permanent)

- Personal history of CRC or adenoma.
- Personal history of inflammatory bowel disease
- Family history of colorectal polyposis, Lynch syndrome or familial CRC (>2 FDR with CRC, or one FDR with CRC diagnosed <60 years of age)
- Severe comorbidity
- Previous colectomy
Exclusion criteria (temporary)

- Previous colorectal examination:
  - Colonoscopy or flexible sigmoidoscopy within 5 years
  - FOBT within 2 years

- Symptoms suggesting colorectal disease (rectal bleeding, abdominal pain, changes in intestinal habits, weight loss, fatigue, etc.)
Sample Size Calculation

- Ten-year rate of death from CRC:
  - Crude: 6.96‰
  - Biennial FIT: 3.41‰ (↓ 51%)
  - One-time Colonoscopy: 1.74‰ (↓ 75%)
- Alpha risk (one-sided): 0.025
- Power (1-beta): 0.20
- Overall compliance rate: 30%
- Non-inferiority: absolute difference ≤2.2‰ in CRC mortality rate at 10 years (intention-to-screen analysis)

27,749 subjects in each group (total: 55,498)
POPULATION SELECTION PROCESS

Target population (CHR)

Lists with name, date of birth, SSN, contact address

- Cancer registries
- Primary care medical records
- Hospital databases

Elimination of subjects with exclusion criteria or deceased

Individuals were clustered by household

Computed generated lists in blocks of 4
RANDOMISATION & INVITATION PROCESS

Randomisation 1:1, stratified by age & sex
(prior to invitation: Zelen design)

- Presentation letter (mail)
  - Information on CRC
  - Benefit of screening
  - Leaflet (screening methods)
  - Rationale of the trial

- Invitation letter (mail)
  - Group assignment & information on the screening option
  - Appointment to LSO

2 weeks
INCLUSION PROCESS

Appointment: Local Screening Office

- To track subjects that did not come to the appointment
- To confirm compliance with inclusion/exclusion criteria
- To provide detailed information of the study
- To obtain written informed consent for participation
- To complete a questionnaire
- To include them in the project database
- To provide a FIT kit (Group I) or a date for colonoscopy (Group II)

Reminder letters (2) if no attending
Specific characteristics

- Cross-over between study groups was allowed
- Incomplete colonoscopy: CT-colonography
- Quality-assurance program:
  - FIT measurements (i.e. daily calib & external validation)
  - Colonoscopy (i.e. bowel cleansing, withdrawal time)
- Online database (www.coloncrib.org)
- Comunication plan
- Analysis by:
  - Intention-to-screen
  - As-screened
Issues encountered

Quality audits

- Observational nested studies:
  1. Modifiable endoscopic factors that influence the ADR in CRC screening colonoscopies
     Jover et al. Gastrointest Endosc 2013
  2. Factors related to the endoscopist
     Jover et al. Endoscopy 2016
  3. Correlation between ADR in primary colonoscopy & FIT
     Cubiella et al. UEG Journal 2017
Inclusion period (1st round)
Group I: FIT
Group II: colonoscopy

June 2009
June 2011

Analysis at Baseline Screening

FIT
FIT
FIT
FIT
Screening (continued)

2018
2021

Analysis of mortality
Analysis of CRC incidence
Cost-efficacy
Participation & Crossover rates

*Intention-to-Screen analysis (interim report)*

**Participation rate**

- Colonoscopy: 24.6%
- FIT: 34.2%

*p = 0.0001*

**Crossover rate**

- Colonoscopy > FIT: 6.2%
- FIT > colonoscopy: 0.40%

*p = 0.0001*

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

OR, 16.8 (95% CI, 13.9-20.2)

*Quintero & Castells et al. NEJM 2012*