

First head-to-head trial of colonoscopy versus faecal testing for colorectal cancer screening



Cancer screening tests can be divided into early detection and preventive tests.¹ Early-detection tests (eg, mammography for breast cancer and prostate-specific antigen testing for prostate cancer) detect cancer early with the aim of reducing cancer mortality. These tests cannot reduce the risk of individuals developing cancer. Preventive screening tests (eg, colonoscopy for colorectal cancer and Papanicolaou-smear cytology for cervical cancer) aim to prevent cancer through the identification of benign cancer precursors for removal. Preventive screening aims to both reduce cancer risk and the risk of cancer-related mortality.¹

Available screening tests for colorectal cancer include both early-detection tests and preventive tests. The most commonly used early-detection test is faecal immunochemical testing. The most commonly used preventive screening test is colonoscopy. The variety of tests provides opportunities for decision making based on societal and personal priorities, values, and preferences.

Care providers might choose a cheaper, repetitive, non-invasive test (such as faecal immunochemical testing every other year) to reduce the risk of people dying from colorectal cancer, or an invasive, more expensive test less often (such as colonoscopy every 10 years), which might also prevent colorectal cancer. To be able to make evidence-based decisions about which test to choose, randomised trials of the comparative benefits of screening tests on colorectal cancer incidence and mortality are needed. However, to date such evidence has not been available.

In *The Lancet*, Antoni Castells and colleagues report the results of COLONPREV, the first randomised trial comparing faecal immunochemical testing and colonoscopy.² In this landmark study, more than 57 000 men and women aged 50–69 years in Spain were randomly assigned to one-time colonoscopy or faecal immunochemical testing every other year. The primary outcome was colorectal cancer mortality at 10 years, and secondary outcomes included colorectal cancer incidence at 10 years. After 10 years, the absolute risk of colorectal cancer mortality was 0.22% among participants in the colonoscopy group compared with

0.24% among those in the faecal immunochemical test group (risk difference –0.02% [95% CI –0.10 to 0.06]). According to these results, faecal immunohistochemical test screening was non-inferior to colonoscopy after 10 years. Colorectal cancer incidence was also similar between the two groups (1.13% for the colonoscopy group vs 1.22% for the faecal immunochemical test group; risk difference –0.09% [95% CI –0.28 to 0.10]).

The COLONPREV trial design was truly population-based. All eligible individuals were randomly assigned regardless of their interest in participating in the assigned intervention. This might explain the low participation rate of 20.1% in the colonoscopy group. In comparison, the participation rate in the faecal immunochemical test group was 33.6% in the first round and declined gradually to 18.5% in the fifth round.² Considering the similarity in rates observed, the reported comparative intention-to-screen analyses should provide reliable estimates for what can be expected when screening is introduced in a country or region.

During the trial period, a faecal immunochemical test screening programme was rolled out in Spain. Reassuringly, contamination was similar in the two groups whereby around 17% of participants who did not participate in trial screening still attended the Spanish screening programme when invited.² In Spain,

Published Online
Month date, 2025
<https://doi.org/10.1016/P11>
See Online/XXX
<https://doi.org/10.1016/P11>



AJ photo via Science Photo Library

colonoscopy screening was not recommended outside of the trial.

Results of the per-protocol analyses, which included all individuals who were screened as per the procedure originally allocated, and the as-screened analyses, which included all individuals who crossed over to the other screening group (crossover was allowed, and more people crossed over from colonoscopy to faecal immunochemical test than from faecal immunochemical test to colonoscopy), are included in the appendix of the Article. In the per-protocol analyses, colorectal cancer mortality was 0.02% in the colonoscopy group and 0.11% in the faecal immunochemical test group (risk difference -0.09 [95% CI -0.17 to -0.02]). We agree with the investigators that the per-protocol and as-screened analyses are difficult to interpret; in a post-hoc analysis, all-cause death was significantly higher in people who did not attend screening than those who did, which implies selection bias.²

The faecal immunochemical test is a so-called triage screening test; people who test positive are referred for colonoscopy. In COLONPREV, 17.7% of people randomly assigned to faecal immunochemical testing were referred for colonoscopy over the five faecal immunochemical test screening rounds. Of all randomly assigned participants, the proportion of people who required a colonoscopy was about a third in the faecal immunochemical testing group compared with the colonoscopy group.

These new estimates on absolute risks complement and extend those observed in a 2022 European trial of colonoscopy versus no screening (NordICC).³ Absolute risks are important for transparent prioritisation in health care, and for individuals when assessing personal priorities for preventive services. The COLONPREV trial provides patients, caregivers, and policy makers with long-awaited evidence to decide which test to choose.

From a societal perspective, since there were no significant differences identified between colonoscopy and faecal immunochemical testing with regard to colorectal cancer incidence and mortality, similar benefits might be derived with one-third of people having colonoscopies. From an individual perspective, these results mean that people can either choose to have one colonoscopy every 10 years or five biennial faecal immunochemical testing with a third of people being likely to require a colonoscopy.

Both the COLONPREV and NordICC³ trials have reported prespecified endpoint assessments for colorectal cancer incidence and mortality after 10 years. Consensus when the studies started was that 10 years is a sufficient follow-up duration to obtain reliable estimates. However, it has been argued that longer follow-up is needed to assess the full potential of colorectal cancer screening tests.⁴ Therefore, it is positive that both the COLONPREV and NordICC investigators plan analyses with longer follow-up.

Two additional randomised trials are in progress: the US CONFIRM trial comparing one-time colonoscopy with annual faecal immunochemical testing and the Swedish SCREESCO trial comparing one-time colonoscopy, biennial faecal immunochemical testing, and no screening.^{5,6} The awaited results of these trials and the results of the longer follow-up from the COLONPREV and NordICC trials might change our understanding of the comparative effectiveness of colorectal cancer screening tests.

Most countries now have population screening programmes for colorectal cancer, so it is unlikely to expect new trials to start. The only way to assess the benefits of new, emerging screening tests are comparative trials embedded in screening programmes.⁷ Some embedded trials are already under way in Norway and Poland (comparing sigmoidoscopy, colonoscopy, and faecal immunochemical testing) and in the Netherlands (comparing 2-year and 3-year faecal immunochemical testing screening intervals).^{7,8}

We declare no competing interests.

***Michael Bretthauer, Mette Kalager**
michael.bretthauer@medisin.uio.no

Clinical Effectiveness Research Group, University of Oslo, Oslo 0372, Norway (MB, MK); Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway (MB, MK)

- 1 Adami H, Kalager M, Bretthauer M. The future of cancer screening—guided without conflicts of interest. *JAMA Intern Med* 2023; **183**: 1047–48.
- 2 Castells A, Quintero E, Bujanda L, et al. Effect of invitation to colonoscopy versus faecal immunochemical test screening on colorectal cancer mortality (COLONPREV): a pragmatic, randomised, controlled, non-inferiority trial. *Lancet* 2025; published online March 27. XXXXXX [Prod: Please add DOI details when known].
- 3 Bretthauer M, Løberg M, Wieszczy P, et al. Effect of colonoscopy screening on risks of colorectal cancer and related death. *N Engl J Med* 2022; **387**: 1547–56.
- 4 Dominitz JA, Robertson DJ. Understanding the results of a randomized trial of screening colonoscopy. *N Engl J Med* 2022; **387**: 1609–11.
- 5 Dominitz JA, Robertson DJ, Ahnen DJ, et al. Colonoscopy vs fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM): rationale for study design. *Am J Gastroenterol* 2017; **112**: 1736–46.

-
- 6 Forsberg A, Westerberg M, Metcalfe C, et al. Once-only colonoscopy or two rounds of faecal immunochemical testing 2 years apart for colorectal cancer screening (SCREESCO): preliminary report of a randomised controlled trial. *Lancet Gastroenterol Hepatol* 2022; **7**: 513–21.
- 7 Kalager M, Bretthauer M. Improving cancer screening programs. *Science* 2020; **367**: 143–44.
- 8 Breekveldt ECH, Toes-Zoutendijk E, de Jonge L, et al. Personalized colorectal cancer screening: study protocol of a mixed-methods study on the effectiveness of tailored intervals based on prior f-Hb concentration in a fit-based colorectal cancer screening program (PERFECT-FIT). *BMC Gastroenterol* 2023; **23**: 45.