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# Interpreting the results from the first randomised controlled trial of colonoscopy: does it save lives?

Kerrington Powell ,<sup>1</sup> Vinay Prasad<sup>2</sup>

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<sup>1</sup>School of Medicine, Texas A&M Health Science Center, Bryan, Texas, USA

<sup>2</sup>Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA

Correspondence to:

Dr Vinay Prasad, Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, USA; vinayak.prasad@ucsf.edu

In screening for colorectal cancer (CRC), colonoscopy is generally referred to as the 'gold standard', as it examines both the right and left colon. Despite wide adoption, colonoscopy had not been studied in randomised fashion until the Northern-European Initiative on Colorectal Cancer (NordICC) trial. NordICC is a pragmatic, registry-based, randomised controlled trial (RCT) of colonoscopy versus no screening in adults between 55 and 64.<sup>1</sup>

In NordICC, 84 000 participants were randomised (1:2) to either an invitation to colonoscopy or usual care, which, at the time of the study, was no CRC screening. The trial found no difference in the risk of death from CRC (0.28% vs 0.31%; risk ratio (RR)=0.90) or any cause (11.03% vs 11.04%; RR=0.99) and a modest reduction in the risk of colon cancer (0.98% vs 1.20%; RR=0.82) at 10 years of follow-up.<sup>1</sup> There are five implications from this study.

## The role of cancer screening

First, the goal of cancer screening is to improve quantity and quality of life (QoL). When it comes to quantity, death from the target cancer is often used as the primary endpoint (as it is here), though elsewhere we have argued that a more appropriate endpoint is all-cause mortality.<sup>2</sup> Unlike CRC death, all-cause mortality weighs competing risks and off-target effects from screening and downstream interventions (eg, harms from adjuvant chemotherapy for stage II disease). NordICC demonstrates that CRC is an infrequent cause of death—just 2.5% of deaths ( $[(157+72)]/[(3036+6079)]$ ) were from colon cancer—and the risk of dying for any reason remained unchanged from screening.

When it comes to quality, some point to NordICC's reduction in CRC incidence as evidence of improved QoL—after all, a CRC diagnosis often necessitates surgery, chemotherapy or both—but investigators have not disclosed what fraction of tumours required colectomy, hemicolectomy and adjuvant chemotherapy by arm, and more importantly, QoL gains have not been demonstrated. It is unclear which CRCs were averted and whether the procedure's risks and complications offset QoL gains. Investigators plan to release these results at the next update.

## Should governments offer colonoscopy?

Second, due to its pragmatic design, NordICC examines a policy-level question: should a nation fund a population-level colonoscopy screening programme? In NordICC, 42% of those offered to receive a colonoscopy complied (the trial was

powered for 50% compliance). Some commentators dismiss the generalisability to nations such as the USA, where CRC screening rates are 60%–70%.<sup>3</sup> However, the 60%–70% rate from the USA is based predominantly on self-reports and modelling.<sup>4</sup> Second, 60.7% of the NordICC trial's Norwegian cohort received screening, yet there was no evidence CRC mortality was improved in this subgroup (ie, no significant interaction testing was reported).<sup>1</sup>

NordICC suggests, at a population level, colonoscopy may not be effective; let alone cost-effective. When dealing with preventive health services, trade-offs must be made, and clinical preventive strategies with the strongest evidence must take precedence.

## Per-protocol analysis: a fair assessment?

Third, because adherence to screening was only 42%, the investigators performed a per-protocol analysis, comparing individuals who received colonoscopies with covariate-matched controls who did not. In this estimate, the risk of CRC death fell to 0.15% in the invited group and 0.30% in the usual-care group.<sup>1</sup> This analysis unfortunately thwarts the very advantage of randomisation, as unmeasured confounders (eg, medical literacy, health engagement and socioeconomic) may now confound the analysis. An alternative method is instrumental variable adjustment, which scales the intention-to-treat effect of colonoscopy to the full population while preserving the advantages of randomisation; this estimate finds no difference in CRC mortality (absolute risk reduction, 0.07%; 95% CI –0.26% to 0.12%).<sup>1,5</sup> In other words, depending on the statistical adjustment strategy used, per-protocol estimates may differ, and whether colonoscopy has a clinically meaningful impact on CRC-related mortality remains unknown. However, the instrumental variable analysis is regarded among many economists as a superior measure for determining the potential outcome if full compliance with screening were achieved.

## Is any screening better than no screening?

Fourth, the US Preventive Services Task Force (USPSTF) currently recommends that any screening test is advisable for CRC, but this is not evidence based. Faecal occult blood testing and flexible sigmoidoscopy (Flex Sig) have each shown reduction in CRC death in RCTs<sup>6</sup>; the latter has also demonstrated a reduction in all-cause death in pooled estimates. Additionally, Flex Sig



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is significantly cheaper than colonoscopy (US\$300/5years vs US\$1216/10years.).<sup>7</sup> While it is intuitive that, procedurally, colonoscopy is at least a Flex Sig, practically this is untrue. In Flex Sig trials, a higher proportion of participants agreed to the less invasive option with easier bowel prep.<sup>8</sup> It may be that the benefit of CRC screening hinges on accruing people on the margin—the person who would agree to Flex Sig—but not colonoscopy.

Moreover, colonoscopy has concerning harms. Although NordICC reported zero instances of colon perforation, a potentially fatal complication, the observed perforation incidence in clinical practice is less than one in a thousand.<sup>9–10</sup> It has been hypothesised that the absence of perforation in NordICC was due in part by the fact that the vast majority of procedures were unsedated, preventing the operator from using more force—a contributing factor to perforation.<sup>11</sup> The use of anaesthesia during colonoscopy varies by location, notably in the USA, where sedated colonoscopy is common.<sup>12</sup> However, this potential relationship, as highlighted by the study's principal investigator,<sup>11</sup> is a matter of speculation and further empirical investigation is necessary.

Based on current evidence, the USPSTF's screening recommendations warrant revision as they continue to disregard different risk/benefit profiles of the various screening methods. At the same time, older screening tests need revisiting. Secular trends in surgical quality have made oncologists question the role of adjuvant chemotherapy. Similarly, as societal attitudes towards illness shift, improvements in reporting haematochezia or thin calibre stools may have reduced the effect size of CRC screening.

### The final verdict on colonoscopy is not yet in

Fifth, some contend that the results of NordICC are due to a low adenoma detection rate (ADR). Adenomas are detected and removed during colonoscopy, and a higher ADR correlates with reduced postcolonoscopy CRC.<sup>13</sup> The ADR rate in NordICC was 30.7% (3 634/11 843), meeting the recommended 30% ADR for males and 20% for females at average risk.<sup>13</sup> However, cohorts such as Sweden reported an ADR of 14.4% (70/486). Additionally, nearly one-third of endoscopists had an ADR below 25%.<sup>8</sup> Thus, NordICC may have failed to capture the effect size of colonoscopy at a national screening programme level by having ADRs in cohorts comparably low to other nations, such as the USAs, where the ADR for adults aged 50 or older is nearly 40.0%.<sup>14</sup> Yet, ADR is a moving target. The same study conducted by Shaukat *et al* found that ADR improved from 33.9% in 2014 to 38.12% in 2018.<sup>14</sup> NordICC accrued patients between 2009 and 2014, during which ADR rates were lower, even in the USA. Thus, some commenters penalise NordICC though it employed ADR rates that were broadly prevalent at the time of the study.

Multiple RCTs evaluating colonoscopy, some against alternative screening tests such as faecal immunochemical test, are underway at the time of this writing.<sup>15–17</sup> Both NordICC and the ongoing trials serve as important references in the present discussion surrounding national health screening initiatives. While we acknowledge the limitations of applying the findings from NordICC to clinical practice, if ongoing studies fail to demonstrate superiority of colonoscopy, colonoscopy's role in cancer screening may need reconsidering.

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**ORCID iD**

Kerrington Powell <http://orcid.org/0000-0001-7067-3559>

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