Intention to probe into the colonoscopy trial: Is it the procedure or the trial that failed?

Kevin B. Knopf[a] and Bishal Gyawali[b,c,d,*]

[a]Institute for Health Policy Studies, University of California, San Francisco, CA, USA
[b]Department of Public Health Sciences, Queen's University, Kingston, Canada
[c]Department of Oncology, Queen's University, Kingston, Canada
[d]Division of Cancer Care and Epidemiology, Queen's University, Kingston, Canada

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The NordICC trial published recently provides the first randomized evidence on the effectiveness of colonoscopy-based colorectal cancer (CRC) screening.[1] Although alternative means of CRC screening with evidence from randomized trials are available, such as flexible sigmoidoscopy or non-invasive fecal occult blood testing (FOBT) or fecal immunological test (FIT), physicians and organizations- specifically in the U.S- have been making strong recommendations for colonoscopy screening based on extrapolation of data from sigmoidoscopy trials and the NordICC trial has created a controversy on whether that is appropriate. In this editorial, we delve into the causes of the controversy and make a case for why this trial should or should not change practice.

NordICC enrolled asymptomatic individuals between 55 and 64 years of age from Poland, Norway, Sweden, and the Netherlands between 2009 and 2014 and randomized them to either receive an invitation for a single screening colonoscopy or not. At 10 years, when analyzed in this entire cohort (intention-to-screen population), the risk of CRC in the screening group was 0.98% versus 1.2% in the no screening group, a statistically significant reduction while the risk of dying from CRC was 0.28% versus 0.32%, which was not statistically significant. However, a catch - at the heart of the controversy- is that only 42% of the individuals invited to screen (11,843 of 28,220 invited) actually did accept the invitation and underwent colonoscopy screening. When the analysis was limited to only these 42% who accepted the invitation in the colonoscopy arm (per-protocol analysis) the risk for CRC-related death was significantly lower- 0.15% versus 0.30%.

Critics of the study have argued that what this study shows is not that colonoscopy screening is ineffective but that an ***invitation*** to undergo a single colonoscopy is not effective in reducing the risk of dying from colorectal cancer. However, the question being asked in this trial is not whether colonoscopy in an individual has benefits but whether health systems in the world will reap benefits by investing in population level colonoscopy-based screening. At a population level, most interventions by definition are just invitations and not mandatory. Hence, that only 42% people accept the invitation to colonoscopy, in itself is a major finding of this trial. Countries across the world can indeed learn from this trial that even in high-income, highly-developed European countries with high-literacy, an invitation to colonoscopy screening is met with 58% rejection.

In addition, including only those who underwent colonoscopy (per-protocol analysis) as opposed to including all who were invited (intention-to-screen analysis) leads to flawed conclusions. One, it voids the purpose of randomization and can introduce bias- are individuals who declined invitation systematically different than those who accepted (socio-economic status, educational status, family history of cancer, having some symptoms already, unknown confounders)? Two, it would assume that the uptake rate for colonoscopy is ideally 100% but that is never the case. Even in the U.S., the uptake rate for colonoscopy in 10 years is around 60%, not 100%.[2]

Even in per-protocol analysis, the touted relative benefit in CRC-mortality of 50% is only 0.15% in absolute terms (0.15% versus 0.30%). It is not straightforward whether all health systems would consider this a meaningful benefit enough to invest in such a campaign. Hence, the logical conclusion to derive from this study is that the acceptance rate for population-based colonoscopy screening invitations is low, and at a population level, doing so doesn't reduce the risk of dying from colorectal cancer and thus, investing in CRC screening with colonoscopy at a population level may not be in the best interest of healthcare systems around the world.

Given these negative results from NordICC, perhaps the healthcare systems should encourage interventions that maybe more palatable to the population, will lead to better acceptance rates, and have better quality data. However, in the wake of these results, some professional organizations maintain that colonoscopy should still be the "gold standard" of screening for CRC without any data to back up that claim. We fear that the public

*Corresponding author. Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute, Queen's University, 10 Stuart Street, Level 2, Kingston, ON, Canada K7L 3N6.
E-mail address: gyawali.bishal@queensu.ca (B. Gyawali).

trust in the system may erode with such claims. And if the public were to delay showing up for diagnostic (as opposed to screening) colonoscopy or forego all means of CRC screening because of the screening colonoscopy debate, that would be very unfortunate disservice to the public.

It's understandable to some extent the confusion in the U.S healthcare system because the concept of population-based cancer screening is foreign for U.S. Furthermore, procedure-based reimbursement system ensures that colonoscopy forms a big source of revenue for endoscopists and hospitals in the U.S. In the U.S, screening is opportunistic primarily by recommendation by their primary physician. At the same time, CRC remains the 2nd most common cause of cancer death in the US. The US Preventive Services Task Force endorses different stool-based and direct visualization tests for CRC screening as "individual shared decisions" related to individual risk and aspects of the test.[3] It is not far-fetched to imagine that the modality of screening recommended for a given patient corresponds to insurance type and coverage.

In several healthcare systems in the world, there are limited resources and other important priorities and competing causes of death. There are tragic delays in appropriate work-up of anemia or blood in stool leading to delayed detection of CRC at an advanced stage.[4] Even in high income countries such as U.S, there are broader disparities in timely access to diagnostic colonoscopies, surgical resection rates, and receipt of timely adjuvant chemotherapy.[5] NordICC shows that investing in colonoscopy screening campaigns may not be in the best interest of healthcare systems. Whether it is in the best interest of an individual, is a decision for the individual to make with their physician after being aware of the risks and benefits.

Contributors

BG conceptualized the study. KK wrote the first draft of the manuscript which was edited and revised by both the authors. Both the authors agree with the submission.

Declaration of interests

Dr. Gyawali declares receiving consulting fees from Vivio Health unrelated to the manuscript. Dr. Knopf declares receiving consulting fees from Vivio Health and having stock options at Cadex Genomics, both unrelated to the manuscript. No other conflicts of interest to disclose.

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