Review Article

Colorectal cancer screening—what does the recent NordICC trial mean for the U.S. population?

Taranika Sarkar Das, Jessica Rauch, Aasma Shaukat

Division of Gastroenterology, NYU Grossman School of Medicine, New York, NY, USA

Contributions: (I) Conception and design: A Shaukat; (II) Administrative support: A Shaukat, J Rauch; (III) Provisions of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of the manuscript: All authors.

Correspondence to: Aasma Shaukat, MD, MPH. Division of Gastroenterology, NYU Grossman School of Medicine, 240 East 38th St., Floor 23, New York, NY 10016, USA. Email: Aasma.shaukat@nyulangone.org.

Abstract: The incidence of colorectal cancer (CRC) has declined over time, though it remains a significant cause of morbidity and mortality in the U.S. It has the third highest incidence in incidence among all cancers and is the second leading cause of cancer death in both men and women. Screening reduces the incidence and mortality from CRC. There are several modalities for CRC screening, but the most common ones are a choice between a non-invasive stool-based test, such as fecal immunochemical testing (FIT) or an invasive endoscopic modality, such as colonoscopy. In the U.S. colonoscopy is the predominant CRC screening modality, with observational studies reporting large reductions in CRC incidence and mortality. Recently, a large randomized controlled trial (RCT) on effectiveness of colonoscopy reported smaller than expected reduction in CRC incidence and no reduction in CRC mortality with colonoscopy screening. Explanations of the lower than expected benefit include low uptake of colonoscopy, short follow-up for mortality endpoints and quality indicators (QIs) for some of the endoscopists participating in the screening colonoscopies. The findings of the study need to be taken in context with other literature on effectiveness of colonoscopy, with the overall message of reassuring patients of the benefits of screening, and colonoscopy. Here, we discuss the latest evidence on colonoscopy screening and it in the context of other screening modalities and the landscape.

Keywords: Colonoscopy; colorectal cancer screening (CRC screening); quality

Received: 02 March 2023; Accepted: 10 August 2023; Published online: 30 August 2023.
doi: 10.21037/tgh-23-20
View this article at: https://dx.doi.org/10.21037/tgh-23-20

Introduction

The incidence of colorectal cancer (CRC) has been decreasing over time, though it continues to be a leading contributor to morbidity and mortality in the U.S. It has the third highest incidence of all cancers. For both men and women, it is the second leading cause of cancer death. Among individuals in the U.S., it is estimated that 53,000 deaths in 2021 were due to CRC. CRC screening is a well-validated method to decrease the incidence of CRC and CRC mortality. Colorectal carcinogenesis is heterogeneous, and CRCs advance through several molecular pathways. The primary pathways of the typical adenoma-carcinoma sequence are driven by the development of chromosomal or microsatellite instability. Approximately 20–30% of CRCs emerge from the serrated polyp pathway, which develops mainly via the CpG island methylation pathway (1).

Current trends in colon cancer

Currents trends in colon cancer in persons ≥55 years

According to trends by American Society of Clinical Oncology (ASCO) and Siegel *et al.* (1,2), CRC incidence has been decreasing for persons 55 years or older in the U.S. over the last 50 years. From 2011 through 2017, cancer incidence rates declined among all racial and ethnic groups,

with the largest decreases in cancer incidence among American Indian and Alaska Native (AIAN) and Blacks (1,2). Blacks had the highest incidence of colon and rectum cancer, at 0.04%, followed by Whites and Hispanics, at 0.036% and 0.033%, respectively (1,2). The AIAN community had the lowest incidence rate of colon and rectum cancers at 0.026% (1,2). Over the same time period, CRC mortality rates decreased in individuals ages 55 and older; data showed an annual decline of 3% in individuals ages 65 years and older and 0.6% in individuals aged 50 to 64 years. Cancer mortality rates also decreased among all racial and ethnic groups, with the steepest decline among Blacks. Nonetheless, Blacks continue to have the highest cancer mortality rate across all racial and ethnic groups (1,2).

Currents trends in colon cancer in persons <55 years

Among adults ages 40 to 54 years, the rate of new CRC increased annually by 0.5% to 1.3% between 2011 and 2017 (1,2). Influenced by trends in non-Hispanic Whites, among individuals under 50 years, CRC incidence increased by approximately 2% annually for tumors in the proximal colon, distal colon, and rectum (1,2). Colon cancer incidence rates increased by 1.0% to 2.4% in adults aged 20 to 39 years. In adults aged 20 to 29 years, rectal cancer incidence rates increased 3.2% annually. The rectal cancer diagnosis rate in adults younger than age 55 doubled from 14.6% to 29.2% (1,2).

The NordICC trial

The NordICC trial was a pragmatic randomized controlled trial (RCT) involving asymptomatic people 55 to 64 years of age taken from population registries in The Netherlands, Norway, Poland, and Sweden from 2009 to 2014. Participants were randomized in a 1:2 ratio to be invited to complete a single screening colonoscopy or to not receive any invitation. Of 28,220 participants invited, 11,843 (42%) accepted the invitation and underwent screening.

At the 10-year follow-up, the risk for CRC in the overall intention-to-treat arm was 0.98% *vs.* 1.2% in the control arm, revealing a significantly lower relative risk of 18%. The risk for CRC-related death was 0.28% in the intention-to-screen population compared to 0.31% in the control arm—this difference was not statistically significant. The risk for all-cause death was similar in the two arms.

Adjusted analyses were conducted to evaluate the effect of screening had all participants undergone screening. These analyses showed a decrease in CRC risk from 1.22% to 0.84%, and the CRC-related death risk decreased from 0.30% to 0.15%. Finally, in the per-protocol analysis, which was comprised of the 11,843 participants who received a colonoscopy, the risk for CRC-related death was 0.15% compared to 0.30%—a 50% lower relative risk; however, the risk for all-cause death was not provided (3).

Study interpretation

When interpreting the findings of the NordICC trial in terms of their representativeness for the U.S., there are four crucial considerations:

Firstly, to preserve randomization and balance known and unknown confounders, the study followed an intention-to-screen trial design, inviting individuals randomized to the colonoscopy arm to undergo screening. However, the uptake of colonoscopy among those invited to participate in screening was only 42%, indicating a low participation rate. In contrast, the randomized Minnesota fecal occult blood screening trial reported adherence of fecal occult blood testing and subsequent colonoscopy of more than 84% (4), indicating a substantially higher participation rate. The reason for low participation in NordICC trial could be attributed to invasive nature of colonoscopy. As those randomized to colonoscopy were included in the denominator irrespective of their completion status, the comparison could demonstrate a diluted effect on the reduction in mortality rate, given the low participation in the colonoscopy arm. The per-protocol analysis or compliance-adjusted estimates revealed that those who participated in the screening protocol had a decrease in CRC incidence of 33–40%. Although this reduction was not as high as anticipated, it was more encouraging than the reported relative risk reduction of 18% in the intention-to-screen arm.

Secondly, decades of research on the subject have shown that colonoscopies are highly provider-dependent, and only those of high quality can detect and eliminate early cancers and premalignant polyps, which offer protection against subsequent CRC risk (5). Consequently, in the U.S., a set of quality indicators (QIs) has been established, which have been validated against the risk of developing CRC in the near future. Among these QIs, the most extensively researched ones are the cecal intubation rate and the adenoma detection rate (ADR). At present, the accepted QIs for cecal intubation rate and ADR stand at 95% and 25%, respectively. With over 15 million colonoscopies

conducted annually in the U.S., they are performed with great proficiency. For the most part, endoscopists in the U.S. who perform this procedure meet and even exceed these benchmarks. In contrast, the endoscopists involved in the NordICC study fell short of these standards. Approximately 30% of endoscopists in the NordICC study did not meet the benchmarks by having an ADR below 25% and a cecal intubation rate under 95%. Moreover, the study only provides information on 35 endoscopists who conducted 30 or more colonoscopies during the trial period, leaving uncertainty on the QIs of other endoscopists who may perform fewer cases. This raises concerns about how applicable the study findings are to endoscopists in the U.S.

Thirdly, the study lacks sufficient statistical power to discern a significant disparity in CRC mortality between the two arms. Colonoscopy can identify premalignant polyps that typically take 8 to 20 years to become cancerous and an additional 5 to 10 years to develop, metastasize, and potentially lead to death. Thus, the expected benefit of reducing mortality from the removal of premalignant polyps is anticipated to be observed over a prolonged period. Due to enrollment ending in 2014 and follow-up in 2020, alongside the awareness that national death registries are commonly 2 years behind, the study's follow-up interval is inadequate to demonstrate a variation in mortality risk. The authors are still following the individuals, and more information on CRC mortality in 5 and 10 years will likely be seen. Hence, it is premature to conclude that there is no improvement in CRC mortality with colonoscopy screening.

Lastly, the component of the study that is perhaps most important is the questionable generalizability to the entire U.S. population. However, a generalizable finding is that asymptomatic individuals invited to undergo an invasive test are likely to have low participation rates, leading to suboptimal screening outcome. The NordICC trial population is relatively homogeneous compared to the U.S. population in terms of race and ethnicity. Additionally, in the NordICC study, individuals were randomized to either colonoscopy or usual care without being informed or given consent. Consequently, the authors lack information on the participants' risk factors, including their body mass index, baseline CRC risk, smoking history, dietary habits, and other lifestyle factors linked to the risk of CRC. In addition, the risk factors for CRC differ significantly among various subgroups in the U.S., affecting CRC risk in different ways. As a result, the benefits observed in the intent-to-screen group may not accurately represent the outcomes for an at-risk population in the U.S.

Taking together the variation and lack of generalizability of endoscopists and colonoscopy practice alongside key missed data points in study design and low adherence to screening in the NordICC patient population, it is difficult to see how the results of the NordICC trial may apply to our practice and patient populations in the U.S. (Appendix 1).

The following sections describe the evidence on various aspects of CRC screening to evaluate the NordICC study in context.

Effectiveness of colonoscopy from observational studies

A study conducted by Nishihara *et al.* (6) of nearly 90,000 patients reported that the CRC-specific mortality rate after 24 years of follow-up was lower in individuals who had least one screening colonoscopy, as opposed to those who had never had a screening colonoscopy (multivariate hazard ratio was 0.57 after polypectomy and 0.44 after negative colonoscopy). It also showed that screening colonoscopies were correlated with decreased CRC mortality for cancers in the proximal and distal colon.

Kahi *et al.* studied an Indiana cohort of 715 patients over 15 years of follow up and found that, in comparison with the general population, screening colonoscopies reduced incidence of CRC by 67% (7).

The National Polyp Study (NPS) (8) evaluated the long-term improvements to CRC mortality with polypectomy. The NPS compared the mortality from CRC among patients with adenomas removed to the expected incidence-based mortality from CRC in the general population and to the observed mortality due to CRC among patients with non-adenomatous polyps. After a median of 15.8 years of follow-up, among 2,602 patients who had adenomas removed, 0.46% of patients died from CRC and 47.8% died of causes other than CRC. Following polypectomy, the standardized incidence-based mortality ratio was 0.47, which suggests a 53% decrease in mortality. Mortality due to CRC was comparable for patients with adenomas after polypectomy and patients with non-adenomatous polyps. The study thus suggested that polypectomy significantly diminished the risk of death from CRC (8). During the 10 years following polyp removal, the risk of death from CRC was reduced to a similar level of an internal concurrent control group of patients with no adenomas (8).

Zauber *et al.* (8) also used a microsimulation model to study the mortality effect in the NPS cohort had the

Table 1 Effectiveness of colonoscopy from observational studies

Study name	Follow-up time	Number of participants	Type of study	Results
Nishihara *et al.*	22 years	88,902	Prospective cohort study	The multivariate hazard ratio for CRC was 0.57 after polypectomy and 0.44 after negative colonoscopy. Reduced mortality from proximal colon cancer was observed after screening colonoscopy (multivariate hazard ratio, 0.47)
Kahi *et al.*	15 years	715	Prospective cohort study	Relative risk reduction in CRC incidence of 67%
Lee *et al.*	12 years	1,251,318	Retrospective cohort study	46% lower risk of CRC 88% relative reduced risk for fatal CRC after 10 years following a negative colonoscopy
Zauber *et al.*	15 years	2,602	Prospective cohort study: microsimulation	Over 53% reduction in mortality following adenoma polypectomy CRC risk in patients with adenomas removed was reduced to a level similar to that of patients with non-adenomatous polyps following 10 years follow-up

CRC, colorectal cancer.

adenomas not been removed. The model found an even bigger decrease in mortality rate due to polypectomy than the analysis with the incidence-based mortality rates. The findings provide reassurance that removing precancerous adenomas decreases the risk of death from CRC in people at higher-than-average risk.

Lee *et al.* conducted a cohort study of 1,251,318 adults within a large health plan in Northern California. All participants were at average risk for CRC. Of 99,166 adults who had a negative screening colonoscopy, the study found a relative reduced risk for CRC incidence of 46% and a relative reduced risk for fatal CRC of 88% (9,10). Information on these studies is summarized in *Table 1*.

Uptake, attendance, and adherence to colonoscopy

The Centers for Disease Control (CDC) recommends an 80% uptake rate for colon cancer screening. However, current adherence rates for non-invasive screening tests range from 43% to 66% and are even lower for colonoscopy. A study comparing attendance of fecal immunochemical testing (FIT) versus colonoscopy found that attendance rates were 32.3% and 26.5%, respectively, when patients were invited to complete a single type of screening (11). In a RCT of 26,703 patients by Quintero *et al.* (12), the participation rate of the FIT group was 34.2%, compared to of the colonoscopy group, which was 24.6% (P<0.001) (12). A cross-sectional study conducted in Hong Kong from August 2019 to December 2020 showed a FIT uptake rate of 43.9% and a colonoscopy completion rate of 26.0% (13).

Race and ethnicity as a factor in low adherence to CRC screening

Many studies indicate that cancer disparities are caused by a mixture of inequalities inside and outside the healthcare system, stemming from racism and discrimination. Non-white racial and ethnic communities are more prone to being uninsured and encountering additional obstacles while seeking medical attention, which can restrict their ability to undergo cancer screening, receive adequate care, and obtain appropriate treatment (14). Consequently, screening rates are lower in uninsured populations. The participation rates for FIT and colonoscopy invitation screening approaches were evaluated through a study conducted at the John Peter Smith Health Network, a safety net health system in Fort Worth and Tarrant County, Texas. All patients were uninsured. Of the patient population sampled, 41% were White, 24% were Black, 29% were Hispanic, and 7% were from other racial/ethnic backgrounds. Compared to the colonoscopy and usual care groups, the FIT group showed significantly greater rates of screening (24.6% *vs.* 12.1% *vs.* 40.7%, respectively) among individuals from White, Black, and Hispanic backgrounds. These differences were statistically significant (P<0.005 for all comparisons) (15).

In a randomized clinical trial conducted by Inadomi *et al.* (16), it was discovered that screening rates for CRC are insufficient, particularly among racial and ethnic minorities. The study materials were produced in multiple

languages, and the research staff was proficient in English, Spanish, Cantonese, and Mandarin. The trial showed that White individuals are more likely to undergo colonoscopy tests, while non-White individuals are more likely to complete stool tests. Furthermore, language preference played a significant role in these differences; Asians who chose to speak Cantonese or Mandarin and Latinos who preferred to speak Spanish had higher screening rates than those from the same racial/ethnic group who preferred English. Adjusting for language preference eliminated the racial disparities in screening rates. Strikingly, there was higher adherence among Asians and Latinos compared to African-Americans. The study confirmed the existence of disparities in screening rates between Blacks and other racial groups. Additionally, the research team identified that recommending colonoscopy as the only CRC screening option contributed to lower screening completion rates, compared to when patients were given a choice between fecal occult blood test (FOBT) and colonoscopy or solely recommended FIT, particularly among ethnic and racial minorities (16). Another study conducted by Blackman *et al.* found that immigrants were more likely to adhere to colonoscopy. They found that immigrants were five times more likely to adhere to overall CRC screening. Screening test completion was 95% for Caribbean immigrants and 90.2% for African immigrants, compared to U.S.-born blacks who had a completion rate of 59.2% ($P<0.001$ for all comparisons) (17).

Among all communities, colonoscopy may not be as well-received or as favored as less invasive tests like FIT. If it results in higher participation rates, screening programs utilizing less-invasive screening options may yield comparable or even superior population effectiveness than population-based colonoscopy screening.

Outreach

The study conducted at John Peter Smith Health Network revealed that screening adherence was notably higher in both the FIT and colonoscopy outreach groups, in comparison to the control group. Screening rates for each group were 40.7%, 24.6%, and 12.1%, respectively. For FIT outreach, CRC identification and advanced ADRs were 0.4% and 0.8%, respectively. For colonoscopy outreach, these rates were 0.4% and 1.3%, respectively. In comparison, the rates were 0.2% and 0.4% for usual care, respectively. This RCT demonstrated the effectiveness of mailed stool-based screening as a strategy for increasing CRC screening adherence. In addition, the study found that approximately 25% of screening-eligible individuals who do not typically access regular health care responded positively to mailed stool-based screening outreach (15).

Summarizing colonoscopy effectiveness in the context of poor adherence and uptake

In a randomized study by Quintero *et al.* (12), participation rates were low in both colonoscopy and FIT groups when subjects were invited to undergo CRC screening. However, the research team observed that participants in the FIT arm were more willing to partake than those in the colonoscopy arm. Most relevant, this paper found that the detection rate of CRC was comparable between FIT and colonoscopy. However, colonoscopy appeared to prevent the development of additional tumors by identifying and removing a greater number of adenomas than the FIT group.

Advanced adenomas often precede the development of CRC, and colonoscopy has been shown to be superior in identifying these lesions, which decreases both the incidence and mortality rate of CRC. Nevertheless, the effectiveness of colonoscopy may be compromised in cases of low adherence rates, as demonstrated in this study, in which the colonoscopy group had lower adherence rates than the FIT group (12).

One interesting finding is the high detection rate of low-risk adenomas with colonoscopy, which have a lower tendency to progress to CRC than advanced adenomas. The guidelines for quality assurance in CRC screening set forth in Europe indicate that patients with one to two small adenomas (less than 10 mm in diameter) are considered to be at low risk. Therefore, these patients can be recommended to continue with the same screening pathway advised for individuals without adenomas. Hence, the lower detection rate of these adenomas in patients who underwent FIT-based screening can be an added benefit, as it can decrease the number of individuals requiring colonoscopy. In turn, this can lessen the time and cost burden on both patients and healthcare systems as well as reduce the occurrence of colonoscopy-related complications (12).

According to a microsimulation model that followed individuals for 15 years, screening adults between the ages of 50 and 79, who possess a 3% risk of developing CRC, through an annual FIT or a single colonoscopy, resulted in a 6 per 1,000 individual reduction in CRC mortality. Additionally, colonoscopy and annual FIT screenings were found to lower CRC incidence by 10 and 4 per 1,000 individuals, respectively (18).

Serrated polyps and proximal polyps are a challenge for colonoscopy

Previous studies have found that colonoscopy has a diminished capacity to reduce the incidence of CRC in the proximal or right colon (19,20). Proximal serrated lesions can be more difficult to visualize than other types of lesions, which has been identified as possibly having a significant role in this limitation.

Various case-control studies have revealed that colonoscopy screening can decrease both distal and proximal CRCs, with a reliably lower reduction observed for the proximal colon (19-21). The reason behind the decreased effectiveness of colonoscopy in reducing CRCs in the proximal colon has been linked to the presence of flat and non-polypoid lesions, which are challenging to see and necessitate different removal techniques. In addition, Kahi *et al.* (22) revealed that a substantial percentage of proximal serrated polyps might not be detected during colonoscopy.

According to a recent study by Burnett-Hartman *et al.*, individuals who underwent colonoscopy screening had a lower risk of developing advanced adenomas but not proximal serrated polyps (23). These findings suggest that patients who have undergone colonoscopy screening may benefit from a protective effect against the risk of advanced adenomas but not against proximal serrated polyps (23).

As proximal serrated lesions may play a role in the development of interval cancers, enhancing the capacity to detect such lesions is imperative to ensuring high-quality colonoscopy. The inclusion of the serrated polyp pathway is a distinguishing feature of the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) model, which has shown that incorporating this pathway can influence the efficacy of both FIT and colonoscopy screening. During a 30-year screening period, the reduction in CRC incidence diminished from 53% when no sessile serrated polyp (SSP)-attributed CRCs were considered to 47% when 30% SSP-attributed CRCs were present, and the decrease in CRC mortality decreased from 70% to 66%. Assuming a FIT participation rate of 40%, the reduction in CRC incidence decreased from 27% when no SSP-attributed CRCs were present to 25% when 30% SSP-attributed CRCs were present, and the reduction in CRC mortality decreased from 37% to 35%. Various studies have reported that FIT is less sensitive in detecting SSPs than conventional adenomas. The sensitivity of FIT in detecting large SSPs (10 mm) has been reported to range from 0% to 16.7% (24).

Adverse events related to colonoscopy

Global trends and future challenges (mortality and rate of hospitalization for colonoscopy)

Colonoscopy is an incredibly safe and low-risk CRC screening method. Nonetheless, bleeding and perforation are possible adverse events from the procedure, with bleeding occurring more commonly than perforation.

Large studies (≥50,000 colonoscopies) conducted since 2000 report that the perforation rate during colonoscopy ranges from 0.005% to 0.085%. According to these studies, post-colonoscopy bleeding has been reported to happen in 0.001% to 0.687% of cases (25). The American Society for Gastrointestinal Endoscopy (ASGE)/American College of Gastroenterology Task Force on Quality in Endoscopy has stated that post-polypectomy bleeding occurs in less than 1% of cases (25). Kavic *et al.* (26) reported that the incidence of hemorrhage during a diagnostic colonoscopy is only 0.03%, with most cases occurring after biopsy. Post-polypectomy bleeding is more common and can be classified as immediate or delayed bleeding based on the time of onset (27,28). The rate of post-polypectomy bleeding (0.98%) is considerably higher compared to cases without polypectomy (0.06%) ($P<0.001$) (29). In a prospective study by Sieg *et al.*, the rate of significant hemorrhage was 0.001% (30). This study was limited to outpatients, and most endoscopies were conducted by experienced endoscopists, which may have contributed to the low incidence rate of bleeding observed. However, two large studies conducted in Germany in 2009 (31,32) included over 200,000 patients. Among asymptomatic patients undergoing screening colonoscopies (269,144 colonoscopies), 0.164% reported bleeding, and the incidence of bleeding increased to 0.8% when a polypectomy was performed (30,31). Another study evaluating 236,087 outpatient colonoscopies identified a bleeding rate of 0.220% (32).

Furthermore, more recent studies conducted in the U.S. have reported a higher incidence rate (33,34). For example, a population-based, matched cohort study by Warren *et al.* published in 2009 found that serious gastrointestinal events, including bleeding or the need for transfusion, occurred in 0.639% of the 53,220 colonoscopies (33). They found that the risk of bleeding was over four times more likely in the polypectomy group (0.87% of colonoscopies) compared to the screening group (0.21% of colonoscopies) (18). However, in another study, there were no significant differences in mortality between the colonoscopy group and the

Table 2 The advantages and disadvantages of colonoscopy screening

Advantages of colonoscopy
• 53% reduction in mortality from CRC
• Direct examination of the colon with immediate therapeutic intervention. Advanced adenomas are detected with higher sensitivity than other screening tools
• Long term effect on mortality reduction is from adenoma removal not the detection of CRC itself
• FIT testing detects CRC with almost equal sensitivity as colonoscopy, however FIT testing does not detect advanced adenomas or adenomas with as much sensitivity
• Detects proximal advanced adenomas, non-polypoid lesions (flat), broad based adenoma, carcinoma *in situ*, and T1 cancer more effectively than any other non-invasive tests
• Only test that reduces mortality from proximal colon cancer
• Completed every 10 years
Disadvantages of colonoscopy
• Invasive
• Resource-heavy
• Patient adherence rates are improved with patient navigation resources and follow-up
• The uptake rate is 26.5% for colonoscopy
• Operator-dependent. Endoscopist skill plays an important role in the effectiveness of screening. Quality Indicators such as cecal intubation rate of 95% and ADR of 25%, should be achieved for a colonoscopy to be considered effective
• Requires extensive bowel preparation
• Requires minimal anesthesia, whereas FIT testing does not require any anesthesia
• Associated with complications including bleeding and perforation
• Colonoscopies can miss small, flat, proximal, and serrated polyps

CRC, colorectal cancer; FIT, fecal immunochemical testing; ADR, adenoma detection rate.

unscreened matched control group (CRC mortality rate was reported as 0.22% for both groups). However, there was a higher overall rate of unplanned hospitalization for the colonoscopy group (2.39%) compared to the control group (2.31%) during the observation period. This may be due to the increased rate of hospitalizations following screening colonoscopy (35). Additional prospective research is necessary to comprehensively assess the risks and benefits of non-diagnostic colonoscopies in elderly patients. According to existing research, patients aged 75 or older are 1.6 times more likely to visit the emergency department and 3.7 times more likely to require hospitalization following colonoscopy (36). The risks and benefits of colonoscopy are summarized in *Table 2*.

Quality metrics of colonoscopy

The QIs for colonoscopy are based on recommendations from the American College of Gastroenterology (ACG) and the ASGE and include the following: (I) ADR; (II) appropriate intervals between colonoscopies performed for screening and surveillance of colorectal neoplasia; (III) cecal intubation rate with photographic documentation; and (IV) withdrawal time.

The adequate detection of colorectal polyps relies on high-quality bowel preparation. Inadequate cleansing can cause the missed detection of flat or subtle polyps. This may significantly impact the efficacy of colonoscopy in the proximal colon, as improper cleansing can reduce the identification of adenomas and sessile serrated lesions (SSLs) (37-40).

Despite adequate bowel preparation, the detection of colorectal polyps can still be challenging in the right colon due to the prevalence of flat and serrated polyps that are difficult to visualize. As a result, missed CRCs and polyps are more frequent in the right colon. Endoscopists can

increase their detection rate of polyps and increase ADR by 5% to 20% (41-45).

Previous research has demonstrated that endoscopists have a greater ability than primary care physicians and surgeons to prevent CRC via colonoscopy due to their higher rates of achieving "complete" examinations, which involve intubating the cecum (46-49).

The experience level of the endoscopist also influences the effectiveness of colonoscopy. For example, a 1% higher ADR, which is a metric that improves with endoscopist skill, is associated with a 3% decrease in interval cancer rate (50,51).

Studies have shown that longer withdrawal times during colonoscopy are correlated with increased (52) detection rates of serrated polyp (53). For instance, Butterly *et al.* (54) found a statistically significant correlation between longer normalized withdrawal time (NWT) and higher rates of polyp detection rate (PDR), ADR, and serrated detection rate (SDR), with the peak detection rates occurring at 9 minutes.

A colonoscopy is considered high quality if it is conducted by a colonoscopist who has a sufficient ADR and who performs complete polyp resection, achieves complete cecal intubation, can detect polyps larger than 5 mm, and provides the patient with risk-based recommendations for repeat colonoscopy intervals (55).

Determining the histologic class (adenoma *vs.* serrated) and identifying features associated with deep submucosal invasion are crucial skills for the modern colonoscopist to assess colorectal polyps and lesions accurately.

Furthermore, the recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer have outlined the quality metrics of malignant polyp resection. A malignant polyp is a type of colorectal polyp that shows the neoplastic invasion of the submucosa without extending into the muscularis propria and is typically flat in appearance.

Expert evaluation of colorectal polyps and lesions using techniques such as dye-based chromoendoscopy or electronic-based image enhancement can help identify features specific to deep submucosal invasion by cancer. Lesions with an invasion depth of ≥1 mm of submucosal invasion are defined as having deep submucosal invasion, which is associated with a high risk of residual cancer and lymph node metastasis after endoscopic resection. On the other hand, lesions with an invasion depth of <1 mm are classified as having superficial submucosal invasion, which is associated with a very low risk of lymph node metastasis (0–4%) as long as other adverse histologic features are absent (56,57). Skilled assessment using dye-based chromoendoscopy or electronic-based image enhancement can help identify lesions with endoscopic features specific for deep submucosal invasion (56,57).

Prior to endoscopic resection, a thorough evaluation of the morphology, surface, and vessel pattern of every colorectal lesion detected during colonoscopy should be conducted to identify any potential submucosal invasion and determine the optimal approach for handling such polyps. Lesions classified as Narrow band imaging International Colorectal Endoscopic classification (NICE) type 3 or Kudo type V [VN (nonstructural) and VI (irregular)] are commonly associated with submucosal invasion, often showing surface ulceration and irregularity.

Polyps that cannot be lifted or raised from the colon wall, known as the non-lifting sign, are also associated with deep submucosal invasion. Malignant polyps are more frequently found in the right colon. Specific handling of the pathology specimen is usually required to accurately measure the depth of submucosal invasion in malignant polyps (56,57).

Current gaps and areas of improvement: efficacy

The clinical effectiveness of screening test options and the potentially negative impact of screening tests in adults under 50 years has not been studied. The effectiveness of screening in patients of younger ages varies depending on a patient's underlying risk for CRC, incidence of CRC in their age group, and variability in test validity and reliability by age. Current data show low adherence to screening in high-CRC risk, vulnerable, and minority populations and overuse among low-risk patients and in those with limited life expectancy.

Additionally, efficient coordination of care among various healthcare providers, including primary care providers, pathologists, anesthesiologists, and other specialists, is crucial for improving patients' health outcomes. Although colonoscopy is the primary screening method, it is just one aspect of the larger system of care that also involves other screening tests and providers. Currently, there is no quality measure in place that specifically targets the rate of colonoscopy completion after a positive stool test. Furthermore, the unnecessary use of monitored anesthesia care can result in complications, especially in elderly or medically compromised patients. Coordination and communication among providers is critical to ensure patients receive appropriate care and minimize potential risks (58). Data indicate room for improvement in the accurate interpretation of pathology results. Specifically, there is variability in the interpretation of serrated lesions,

which are associated with an increased risk of colorectal (58).

Improving uptake to meet the CDC goal of 80% screening rate

Solutions to cost barriers with CRC screening

Barthold *et al.* found that out-of-pocket costs can create financial hardships and hinder the completion of the screening process for many patients who test positive on invasive tests. They compared outcomes in states that abandoned patient cost-sharing of follow-up colonoscopy (Kentucky, California, Oregon) with those of neighboring states without such regulations. They discovered that access to full coverage for screening significantly improved overall CRC screening rates (59).

A clinical trial conducted in China compared participation rates of colonoscopy, FIT, and a risk-adapted approach to screening. In the trial's risk adapted approach group, patients were referred to colonoscopy if they were considered high CRC risk and to FIT testing if they were considered low CRC risk. The participation rates were 42.4% for the colonoscopy group, 99.3% for the FIT group, and 89.2% for the risk-adapted group. This suggests that the risk-adapted approach is a feasible and cost-effective method for population-based CRC screening, which could be combined with the well-established one-time colonoscopy and annual repeated FIT screening strategies (60).

Patient navigation assistance

In a randomized clinical trial involving nearly 900 low-income adults, the completion rate for colonoscopy was significantly higher among patients who received navigation assistance (61.1%) compared to those who received usual care in the control group (53.2%, P=0.021) (61-63). Culturally targeted patient navigation systems can further improve screening uptake through patient navigation (62).

According to Sadowski *et al.*, the use of indication labels and patient navigation assistance after a positive FIT screening resulted in a 57.1% increase in timely diagnostic colonoscopy (64). Also, around 25% of individuals eligible for screening who do not access regular health care respond to screening outreach (59).

The studies above demonstrate the importance of implementing systems-based solutions to decrease the financial burden of screening and enhance patient navigation, ultimately leading to increased screening adherence (64,65).

Ongoing and further studies

Currently, RCTs are being conducted in Spain and the U.S. (CONFIRM—Colonoscopy versus Fecal Immunochemical Test in Reducing Mortality from Colorectal Cancer) to compare the effectiveness of stool-based testing and colonoscopy screening. The COLONPREV trial in Spain is a non-inferiority trial that compares stool-based testing with colonoscopy screening. On the other hand, the veterans administration (VA) CONFIRM trial is a superiority trial that compares colonoscopy with an annual FIT screening program. The current guidelines suggest surveillance colonoscopies following polypectomy based on the characteristics and number of identified polyps, but there is a limited amount of evidence supporting these guidelines. The European Polyp Surveillance trial incorporates two randomized trials and one observational study that aim to evaluate evidence-based surveillance strategies after polyp removal (66).

Conclusions

This review paper evaluated the relevance of the results of the NordICC trial for patients in the U.S. as well as provided a comprehensive analysis of the factors affecting CRC screening participation and the impact of CRC screening on morbidity and mortality. While the NordICC trial reported relatively similar rates of CRC mortality between patients invited to complete a colonoscopy and the control group, these findings lack generalizability to the U.S. for a handful of reasons. Decades of research conducted in the U.S. indicate a significant improvement in CRC incidence and mortality with the use of colonoscopy. Studies evaluating the effect of population-based screening efforts for U.S. cohorts should model typical screening uptake rates, QIs for ADR and cecal intubation rate, contain an adequate follow-up timeline, and resemble the population demographics and varied risk factors in U.S. subpopulations. The literature review indicated that screening adherence rates can be improved through patient outreach and by offering less invasive screening methods, such as FIT. Additionally, language, birth place, costs, care navigation obstacles, and lack of access to routine medical care are all factors that impact a patient's willingness to proceed with colonoscopy or fecal-based screening options. These findings can help with the optimization of population-

based CRC screening programs to address the needs, risk factors, and barriers of the patient populations served.

Promising results have emerged from pilot studies of upcoming new tests like the blood-based mSEPT9 test and cell-free DNA, indicating their potential for future implementation. The integration of artificial intelligence (AI) and machine learning will play a crucial role for effective population-based screening.

Moreover, a growing array of image-based tests shows potential to become viable alternatives to colonoscopy in the near future. Among these modalities under development are colon capsule endoscopy (CCE), computed tomography (CT) capsule, and magnetic resonance (MR) colonography. These advancements hold promise in revolutionizing colorectal screening approaches in the coming years.

Acknowledgments

Funding: This study was supported by Steve and Alex Cohen Foundation #001-1 (to AS).

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Muhammad Aziz, Zubair Khan and Viveksandeep Thoguluva Chandrasekar) for the series "Colonoscopy: Updates and Prospects" published in *Translational Gastroenterology and Hepatology*. The article has undergone external peer review.

Peer Review File: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-20/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-20/coif). The series "Colonoscopy: Updates and Prospects" was commissioned by the editorial office without any funding or sponsorship. AS received funding support from Steve and Alex Cohen Foundation (No. #001-1). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin 2020;70:145-64.
2. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. J Natl Cancer Inst 2017;109:djw322.
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. Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. N Engl J Med 2013;369:1106-14.
5. Young PE, Womeldorph CM. Colonoscopy for colorectal cancer screening. J Cancer 2013;4:217-26.
6. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095-105.
7. Kahi CJ, Imperiale TF, Juliar BE, et al. Effect of screening colonoscopy on colorectal cancer incidence and mortality. Clin Gastroenterol Hepatol 2009;7:770-5; quiz 711.
8. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687-96.
9. Lee JK, Jensen CD, Levin TR, et al. Long-term Risk of Colorectal Cancer and Related Deaths After a Colonoscopy With Normal Findings. JAMA Intern Med 2019;179:153-60.
10. Brenner H, Altenhofen L, Stock C, et al. Incidence of colorectal adenomas: birth cohort analysis among 4.3 million participants of screening colonoscopy. Cancer Epidemiol Biomarkers Prev 2014;23:1920-7.
11. Segnan N, Senore C, Andreoni B, et al. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. Gastroenterology 2007;132:2304-12.
12. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706.

13. Chan DNS, Choi KC, Au DWH, et al. Identifying the factors promoting colorectal cancer screening uptake in Hong Kong using Andersen's behavioural model of health services use. BMC Public Health 2022;22:1228.
14. Tong M, Hill L, Artiga S. Racial Disparities in Cancer Outcomes, Screening, and Treatment. Kaiser Family Foundation. 2022.
15. Gupta S, Halm EA, Rockey DC, et al. Comparative effectiveness of fecal immunochemical test outreach, colonoscopy outreach, and usual care for boosting colorectal cancer screening among the underserved: a randomized clinical trial. JAMA Intern Med 2013;173:1725-32.
16. Inadomi JM, Vijan S, Janz NK, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med 2012;172:575-82.
17. Blackman EL, Ragin C, Jones RM. Colorectal Cancer Screening Prevalence and Adherence for the Cancer Prevention Project of Philadelphia (CAP3) Participants Who Self-Identify as Black. Front Oncol 2021;11:690718.
18. Buskermolen M, Cenin DR, Helsingen LM, et al. Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a microsimulation modelling study. BMJ 2019;367:l5383.
19. Baxter NN, Warren JL, Barrett MJ, et al. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. J Clin Oncol 2012;30:2664-9.
20. Doubeni CA, Weinmann S, Adams K, et al. Screening colonoscopy and risk for incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study. Ann Intern Med 2013;158:312-20.
21. Brenner H, Chang-Claude J, Seiler CM, et al. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med 2011;154:22-30.
22. Kahi CJ, Hewett DG, Norton DL, et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol 2011;9:42-6.
23. Burnett-Hartman AN, Newcomb PA, Phipps AI, et al. Colorectal endoscopy, advanced adenomas, and sessile serrated polyps: implications for proximal colon cancer. Am J Gastroenterol 2012;107:1213-9.
24. Greuter MJ, Xu XM, Lew JB, et al. Modeling the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA). Risk Anal 2014;34:889-910.
25. Kim SY, Kim HS, Park HJ. Adverse events related to colonoscopy: Global trends and future challenges. World J Gastroenterol 2019;25:190-204.
26. Kavic SM, Basson MD. Complications of endoscopy. Am J Surg 2001;181:319-32.
27. ASGE Standards of Practice Committee; Fisher DA, Maple JT, et al. Complications of colonoscopy. Gastrointest Endosc 2011;74:745-52.
28. Sorbi D, Norton I, Conio M, et al. Postpolypectomy lower GI bleeding: descriptive analysis. Gastrointest Endosc 2000;51:690-6.
29. Reumkens A, Rondagh EJ, Bakker CM, et al. Post-Colonoscopy Complications: A Systematic Review, Time Trends, and Meta-Analysis of Population-Based Studies. Am J Gastroenterol 2016;111:1092-101.
30. Sieg A, Hachmoeller-Eisenbach U, Eisenbach T. Prospective evaluation of complications in outpatient GI endoscopy: a survey among German gastroenterologists. Gastrointest Endosc 2001;53:620-7.
31. Bokemeyer B, Bock H, Hüppe D, et al. Screening colonoscopy for colorectal cancer prevention: results from a German online registry on 269000 cases. Eur J Gastroenterol Hepatol 2009;21:650-5.
32. Crispin A, Birkner B, Munte A, et al. Process quality and incidence of acute complications in a series of more than 230,000 outpatient colonoscopies. Endoscopy 2009;41:1018-25.
33. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med 2009;150:849-57, W152.
34. Zafar HM, Harhay MO, Yang J, et al. Adverse events Following Computed Tomographic Colonography compared to Optical Colonoscopy in the Elderly. Prev Med Rep 2014;1:3-8.
35. Kobiela J, Spychalski P, Wieszczy P, et al. Mortality and Rate of Hospitalization in a Colonoscopy Screening Program From a Randomized Health Services Study. Clin Gastroenterol Hepatol 2020;18:1501-8.e3.
36. Grossberg LB, Papamichael K, Leffler DA, et al. Patients over Age 75 Are at Increased Risk of Emergency Department Visit and Hospitalization Following Colonoscopy. Dig Dis Sci 2020;65:1964-70.
37. Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc 2003;58:76-9.
38. Froehlich F, Wietlisbach V, Gonvers JJ, et al. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. Gastrointest Endosc 2005;61:378-84.

39. Clark BT, Laine L. High-quality Bowel Preparation Is Required for Detection of Sessile Serrated Polyps. Clin Gastroenterol Hepatol 2016;14:1155-62.
40. Chokshi RV, Hovis CE, Hollander T, et al. Prevalence of missed adenomas in patients with inadequate bowel preparation on screening colonoscopy. Gastrointest Endosc 2012;75:1197-203.
41. Crockett SD, Nagtegaal ID. Terminology, Molecular Features, Epidemiology, and Management of Serrated Colorectal Neoplasia. Gastroenterology 2019;157:949-66.e4.
42. Soetikno RM, Kaltenbach T, Rouse RV, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA 2008;299:1027-35.
43. Hewett DG, Rex DK. Miss rate of right-sided colon examination during colonoscopy defined by retroflexion: an observational study. Gastrointest Endosc 2011;74:246-52.
44. Tang RSY, Lee JWJ, Chang LC, et al. Two vs One Forward View Examination of Right Colon on Adenoma Detection: An International Multicenter Randomized Trial. Clin Gastroenterol Hepatol 2022;20:372-80.e2.
45. Keswani RN, Crockett SD, Calderwood AH. AGA Clinical Practice Update on Strategies to Improve Quality of Screening and Surveillance Colonoscopy: Expert Review. Gastroenterology 2021;161:701-11.
46. Singh H, Nugent Z, Demers AA, et al. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. Gastroenterology 2010;139:1128-37.
47. Rex DK, Rahmani EY, Haseman JH, et al. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. Gastroenterology 1997;112:17-23.
48. Baxter NN, Sutradhar R, Forbes SS, et al. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. Gastroenterology 2011;140:65-72.
49. Rabeneck L, Paszat LF, Saskin R. Endoscopist specialty is associated with incident colorectal cancer after a negative colonoscopy. Clin Gastroenterol Hepatol 2010;8:275-9.
50. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370:1298-306.
51. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010;362:1795-803.
52. Liang J, Kalady MF, Appau K, et al. Serrated polyp detection rate during screening colonoscopy. Colorectal Dis 2012;14:1323-7.
53. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Differences in proximal serrated polyp detection among endoscopists are associated with variability in withdrawal time. Gastrointest Endosc 2013;77:617-23.
54. Butterly L, Robinson CM, Anderson JC, et al. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire Colonoscopy Registry. Am J Gastroenterol 2014;109:417-26.
55. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc 2020;91:463-85.e5.
56. Shaukat A, Kaltenbach T, Dominitz JA, et al. Endoscopic Recognition and Management Strategies for Malignant Colorectal Polyps: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc 2020;92:997-1015.e1.
57. Seitz U, Bohnacker S, Seewald S, et al. Is endoscopic polypectomy an adequate therapy for malignant colorectal adenomas? Presentation of 114 patients and review of the literature. Dis Colon Rectum 2004;47:1789-97.
58. Komanduri S, Dominitz JA, Rabeneck L, et al. AGA White Paper: Challenges and Gaps in Innovation for the Performance of Colonoscopy for Screening and Surveillance of Colorectal Cancer. Clin Gastroenterol Hepatol 2022;20:2198-209.e3.
59. Barthold D, Yeung K, Lieberman D, et al. Comparison of Screening Colonoscopy Rates After Positive Noninvasive Testing for Colorectal Cancer in States With and Without Cost-Sharing. JAMA Netw Open 2022;5:e2216910.
60. Chen H, Shi J, Lu M, et al. Comparison of Colonoscopy, Fecal Immunochemical Test, and Risk-Adapted Approach in a Colorectal Cancer Screening Trial (TARGET-C). Clin Gastroenterol Hepatol 2023;21:808-18.
61. DeGroff A, Schroy PC 3rd, Morrissey KG, et al. Patient Navigation for Colonoscopy Completion: Results of an RCT. Am J Prev Med 2017;53:363-72.
62. Jandorf L, Cooperman JL, Stossel LM, et al. Implementation of culturally targeted patient navigation system for screening colonoscopy in a direct referral system. Health Educ Res 2013;28:803-15.
63. Escoffery C, Fernandez ME, Vernon SW, et al. Patient Navigation in a Colorectal Cancer Screening Program. J Public Health Manag Pract 2015;21:433-40.

64. Sadowski BW, Bush AM, Humes R, et al. Systems-based Strategies Improve Positive Screening Fecal Immunochemical Testing Follow-up and Reduce Time to Diagnostic Colonoscopy. Mil Med 2022;187:e554-7.
65. Ding H, Lin J, Xu Z, et al. A Global Evaluation of the Performance Indicators of Colorectal Cancer Screening with Fecal Immunochemical Tests and Colonoscopy: A Systematic Review and Meta-Analysis. Cancers (Basel) 2022;14:1073.
66. Jover R, Bretthauer M, Dekker E, et al. Rationale and design of the European Polyp Surveillance (EPoS) trials. Endoscopy 2016;48:571-8.

doi: 10.21037/tgh-23-20
Cite this article as: Das TS, Rauch J, Shaukat A. Colorectal cancer screening—what does the recent NordICC trial mean for the U.S. population? Transl Gastroenterol Hepatol 2023;8:40.