Attribution of Colonoscopy Risk Does Not FIT! Reply

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colorectal cancer (CRC) screening programs is inadequate because of limitations in the reporting of colonoscopy morbidity and mortality.[1] They are to be commended for having undertaken an extensive effort to fill this void with research involving their sophisticated national registry. Although the authors make the important point that the benefit of FIT exceeds the risk of harm, their report implies that the harm profile of FIT must incorporate the morbidity and mortality risk of colonoscopy. The distinction between association and causation is important, and others may mistakenly interpret the study to suggest that FIT screening is directly responsible for subsequent colonoscopy complications. This is the equivalent of overstating the risk of ground transportation to the airport by including the risk of flying in an aircraft even when no flight is taken.

FIT, multitarget stool DNA, blood and urine DNA markers, and other CRC screening programs have proven value in diagnosis and prevention. Although colonoscopy is frequently performed to evaluate a positive FIT or other CRC screening test, other less invasive alternatives (eg, computed tomography colonography/virtual colonoscopy, capsule colonoscopy, multitarget DNA, double contrast barium) are available, and may be preferred based on risk stratification. Although colonoscopy has advantages of direct visualization, biopsy, and polypectomy, it does have disadvantages that have challenged its claim to be the gold standard of CRC screening. Among these are high expense, unpleasant and often inadequate bowel cleansing, limited access and high use of resources, variable quality of colonoscopists, frequent anatomic limitations of visualization of the colonic mucosa, limited reproducibility, and disparity of accuracy by gender.

Morbidity includes bleeding, perforation, infection, cardiopulmonary and cerebrovascular compromise, missed cancer and polyp diagnosis, inadequate polyp resection, lost polypectomy specimens, splenic injury, anesthesia complications, and metachronous tumor seeding.[2-8] Mortality may be underreported as the authors have identified in their national registry. Identification of risk stratification factors, such as anticoagulation and antiplatelet therapy, therapeutic and diagnostic studies, age, colonoscopist training, facility volume, and comorbidities, such as cardiovascular and pulmonary compromise, may reduce the risk of complications.

The use of FIT for CRC screening is cost-effective, accessible, rapid, reproducible, and safe. Using FIT as the primary CRC screening reduces the use of colonoscopy and the actual number of individuals impacted by the morbidity and mortality of CRC screening. The identification of CRC when compliant with an annual FIT screening program is comparable with colonoscopy screening. The rate of false-positive and -negative FIT results is well documented in the literature and compares favorably with other CRC screening approaches. The potential harm of a positive FIT from colonoscopy complications is more than counterbalanced by the avoidance of colonoscopy complications when the FIT screening is negative.

Diagnostic and therapeutic colonoscopy remains the worldwide standard, yet its use as the primary CRC screening modality is primarily limited to the United States. Besides the population-based socioeconomic benefits, using noninvasive CRC screening methods and reserving colonoscopy for diagnosis and therapy can substantially reduce the burden of morbidity and mortality. Further refinements and advances in noninvasive CRC screening, such as blood tests under development that identify DNA from cancer and polyps, will lead to ever-greater compliance with safe, accurate, cost-effective screening. The earlier identification of polyps and cancers, with reallocation of limited colonoscopy resources to diagnosis, therapy, and prevention, will advance the effort to address this major public health concern.

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Conflicts of interest
The authors disclose no conflicts.

Most current article

https://doi.org/10.1016/j.cgh.2021.07.042

Reply. In a recent publication on colonoscopy-related mortality in a fecal immunochemical test (FIT)-based colorectal cancer screening program we estimated the occurrence of fatal adverse events caused by colonoscopy as follow-up of a positive FIT result.[1] In response to our findings, Weiss and colleagues stated that the complications by follow-up colonoscopy after positive FIT should not be

attributed to FIT screening, because other less invasive follow-up alternatives are available.

Although technically complications related to colonoscopy or other follow-up alternatives are not caused by the FIT itself, we strongly believe that screening should not be seen as the primary screening test but also include its consequential events. When comparing screening strategies, we aim to include the harms and benefits of the entire screening process. We attribute the estimated 33% colorectal cancer–related mortality reduction to FIT screening, yet this can only be accomplished through the follow-up colonoscopy.[2] Simply doing the FIT does not result in any benefit. When possible, an "intention-to-treat" approach is preferred to realistically estimate the beneficial effects and risks of a certain screening strategy. This also accounts for providing information to potential screening participants. We firmly believe that invitees for a FIT-based screening program should be informed at time of invitation on the potential risks of the follow-up diagnostic test when the FIT turns out positive.

The authors argue that other diagnostic tests than colonoscopy could be considered for follow-up after a positive FIT. Yet, we would like to contest this view. Currently most colorectal cancer screening programs, if not all, use colonoscopy as primary screening test or to evaluate a positive screening (eg, stool-based screening or sigmoidoscopy screening).[3] In the Netherlands, FIT-positive participants are invited for a precolonoscopy intake to estimate their eligibility for undergoing colonoscopy. Between 2014 and 2016, 93% of the FIT-positive participants were advised to undergo colonoscopy based on this intake, and 2% to undergo computed tomography colonography,[4] which is often the only alternative diagnostic test in population-based screening programs. Although Liedenbaum et al[5] showed that computed tomography colonography after a positive FIT could have similar accuracy for detecting lesions >10 mm as colonoscopy (93% vs 97%), it was less sensitive for lesions between 6 and 9 mm (78% vs 97%). Also, because of the high prevalence of adenomas or colorectal cancer in the FIT-positive population (70%), most (72%) of the individuals that underwent computed tomography colonography still needed colonoscopy for further follow-up.[6] This shows the dominant role of colonoscopy as evaluation of a positive FIT result and demonstrates the limited use of other methods in screening programs. Nevertheless, whenever these alternatives become more popular in the future, the impact by such development on the harms of screening should not be overlooked when comparing screening strategies.

Weiss and colleagues propose risk stratification to offer individuals with a high risk for colonoscopy complications a less-invasive alternative as triage instrument. We agree that this could lower the rate of colonoscopy complications and thus prevent fatal adverse events. However, these high-risk individuals would constitute a very small proportion of the presumptively healthy screening population with a positive FIT result and even then, the larger part still undergoes colonoscopy when the triage instrument confirms the increased risk for colorectal neoplasia. This makes that the impact of selective triaging on the colonoscopy-related mortality after positive FIT is in our opinion negligible and should not be a reason to separate the risk for colonoscopy complications from FIT screening.

Because colonoscopy is such an integral part of FIT screening and crucial for achieving the intended colorectal cancer mortality reduction, we consider its (low) risk for complications inseparable of the FIT. Nevertheless, we strongly agree with Weiss and colleagues that FIT screening compares favorably with other colorectal cancer screening approaches and that its benefits vastly outweigh the potential harms.

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Conflicts of interest
The authors disclose no conflicts.

Most current article
https://doi.org/10.1016/j.cgh.2021.09.012

Perinatal Risk Factors for Pediatric Nonalcoholic Fatty Liver Disease: Impact of Inborn Errors of Metabolism

Dear Editor:

We read with great interest the systematic review on perinatal risk factors for pediatric nonalcoholic fatty liver disease by Querter et al.[1] Nonalcoholic fatty liver disease is a leading cause of chronic liver disease in children,[2] and attempts to identify potential risk factors are important. The authors found that maternal body mass