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EBM opinion and debate

Colorectal cancer screening at a younger age: pitfalls in the model-based recommendation of the USPSTF

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Over the last 15 years, there have been dramatic changes in colorectal cancer (CRC) screening guidelines by the US Preventive Services Task Force (USPSTF). In 2008, grade A USPSTF screening recommendations for CRC suggested adults aged 50–75 receive either a flexible sigmoidoscopy (FS), faecal occult blood test (FOBT) or colonoscopy.[1] In 2016, the USPSTF expanded the screening recommendations to include faecal immunochemical tests (FITs) and blood-based cancer screening for methylated SEPT9 DNA,[2] the latter of which is theorised to improve screening rates owing to its non-invasive nature and preference over stool testing.[3] At the time, editorialists addressed the limited clinical utility of these modalities compared with conventional FOBT, notably the inferior predictive value and potential indication drift of serology tests.[4] Since the addition of these more uncertain screening tests, the debate has centred on whether expanding options will improve outcomes by drawing more participants or whether additional options will lead to worse outcomes by diverting people towards less effective methods.

Most recently, in 2021, the USPSTF took the additional step of using a model to extrapolate the lower limit of recommended screening to 45 years of age.[5] These panel decisions seem to be more liberal in their approach to cancer screening, but they may actually lead to unanticipated outcomes, and there is currently little reliable evidence to establish if these recommendations are beneficial. As a result, two critical issues arise[1]: What are the potential consequences of making national clinical care recommendations based on lower levels of evidence?[2] Is it appropriate for age cut-offs to be lowered based on modelling?

The purpose of providing more screening options is ostensibly to increase the fraction of people who choose at least one option over no screening at all. However, it is likely that some people who would otherwise have selected the more effective or proven screening method (eg, endoscopy) will choose a poorer alternative (eg, blood-based screening) out of convenience. To date, studies have measured the sensitivity and specificity of blood-based tests but have not demonstrated an effect on stringent clinical outcomes such as colorectal incidence or disease-specific mortality (table 1).[6] This becomes problematic since screening tests and patient outcomes are not necessarily tied together. In other words, showing that a screening technique can detect cancer does not indicate that it is capable of lowering disease-specific mortality.[4]

Second, if the USPSTF is to rely on modelling, we must acknowledge the limitations of this methodology, which is that modelling can be erroneous.[7 8] The unreliability of models is even more apparent in regard to screening efforts because they inherently attempt to simplify immensely complex biological processes. Seven different models, for example, indicate a range of a 28%–65% decrease in breast cancer mortality that may be ascribed to

Table 1 Description of the quality of evidence demonstrating effectiveness of screening in reducing colorectal incidence and/or death[6]

Screening test	Description
Flexible sigmoidoscopy	Four randomised controlled trials (n=458 002) showed that flexible sigmoidoscopy reduced CRC incidence and death compared with no screening.
GFOBT*	Five randomised controlled trials (n=689 259) demonstrated that gFOBT reduced CRC incidence and death compared with no screening. One of these studies is still ongoing, but interim findings have aided in determining gFOBT's effectiveness. Additionally, one clinical trial (n=91 199) also demonstrated that gFOBT may reduce CRC incidence and death compared with no screening.
Faecal Immunochemical Test†‡	One large, prospective observational study (n=5 417 699) showed an associative reduction in CRC mortality compared with no screening.
Colonoscopy	Two prospective observational studies (n=436 927) indicate that colonoscopy may help decrease the incidence and death from CRC.

Created by the authors.
*Hemoccult II (Beckman Coulter).
†OC-Sensor (Eiken Chemical).
‡HMJACK (Kyowa Medex).
CRC, colorectal cancer; gFOBT, Guaiac Faecal Occult Blood Test.

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screening.[7 8] Because modelling may produce large variations in estimates and is highly reliant on underlying assumptions, efforts have been undertaken to establish criteria for evaluating the methodological rigour of these models to determine if their outputs (ie, evidence) are reliable. One such effort is the Grading of Recommendations Assessment, Development and Evaluation approach.[9] However, modelling still does not effectively capture the long-term negative implications of cancer screening (eg, overdiagnosis, false positives) or the fact that tumours develop and sometimes regress at different rates.[7] In other words, tumour progression is not ubiquitous; it varies, and to usher national guidelines based on data assumptions from observed trends, historical controls, and most importantly, lacking trials on the 'effect of screening among asymptomatic adults aged 45–49,' should be exercised with caution.[5] Proponents of the age expansion will argue that the only danger associated with early screening is the extra cost, however, this argument ignores risks related to anaesthesia, procedures, colonoscopic perforation and preparative laxative treatments, and the potential fact that removing polyps in these age groups (as opposed to removing them at age 50), does not result in a net benefit.

Without randomised control trials, the actual benefit–harm ratio, as well as perforation and complication rates, may never be determined. Presenting the data in the form of a number needed to screen is especially important in this context because doing otherwise (ie, without communicating baseline risk) conveys an inflated benefit without considering harms. For instance, though all of the modalities in the table 1 have shown a reduction in CRC mortality, only FS has shown a reduction in all-cause mortality.[10] Even when we examine CRC-related deaths, which are reduced more than deaths from all causes, it takes around 10 years for individuals aged 50–74 to see a CRC death averted for every 1000 FS screenings.[11] This benefit must be contrasted against risks, such as perforation, which occurs at a rate of 1 in 1400 for colonoscopies,[12] or other serious adverse events, which occurs at a rate of 1–19 in 10 000 for FS,[11] that results in a colostomy, infection or death which may undermine any benefit in terms of quality of life and well-being gained from screening.

Moreover, there is no apparent reason why 45 is the starting age. Why not go down to 30? According to data recently presented at digestive disease week, the incidence of all neoplastic findings was over 15% for 30–34-years.[13] Until the findings of randomised trials are available, age cut-offs will remain arbitrary, and the adage that '45 is the new 50'[13] will remain meritless rhetoric. An equally reasonable counterargument may be made that age extension will decrease the yield and value of screening and cause unnecessary harm to patients. Age extension may even have the effect of shifting the focus away from older groups and towards younger ones, resulting in unintended consequences. The age extension also does not account for patients' values and preferences, which remains a grey area in terms of the degree of benefit required for people to opt-in screening.[14] Given the broad variation in preferences, perhaps the USPSTF should examine patient values before extending the age recommendation if the objective is to improve screening participation and adherence. However, none of these appeals to reason will be realised without conducting prospective studies to tease out uncertainty.

Without randomised trials, we have to ask: How well do the model-based estimates represent the real world? In the modelling study, perfect adherence was assumed with all screening.[5] Although the researchers deduce the consequences of non-compliance, exalting models to estimate life-years gained or lost as a result of screening compliance is hypothetical and does not serve patient groups who stand to benefit the most from CRC screening (ages 50–69), particularly given that many individuals this age are not currently screened appropriately.[15] Because there is insufficient data to leverage, models are incapable of reflecting the potential for population outcomes to worsen due to age expansion. Even randomised trials, our current gold standard of evidence, are not entirely representative of clinical practice due to the fact they often enrol patients different than average clinic patients.[7] Yet, at the very least, we should be using the most compelling evidence collecting methods available, particularly for questions concerning well-individuals, who by definition cannot feel better than they already do.

Finally, randomised trials for cancer screening have become underused. Conducting these studies on younger patient populations with new screening techniques will require significant resources and time. Put differently; it will be difficult, but not as difficult as solving the potential consequences that models cannot predict. While it is tragic to lose young adults to CRC, let alone any ailment, adopting national recommendations before randomisation may subject them to medicalisation without countervailing benefits. As healthcare professionals, we must remain objective before adopting guidelines based on emotional appeals and weak data. By remaining evidential, we develop greater empathy for our patients by offering them effective screening techniques or abstaining them from procedures that do not improve outcomes.

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