# Optimizing the Quality of Colorectal Cancer Screening Worldwide

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**Abstract**

Screening, followed by colonoscopic polypectomy (or surgery for malignant lesions), prevents incident colorectal cancer and mortality. However, there are variations in effective application of nearly every aspect of the screening process. Screening is a multistep process, and failure in any of single step could result in unnecessary morbidity and mortality. Awareness of variations in operator- and system-dependent performance has led to detailed, comprehensive recommendations in the United States and Europe on how colonoscopy screening should be performed and measured. Likewise, guidance has been provided on quality assurance for non-primary colonoscopy-based screening programs, including strategies to maximize adherence. Quality improvement is now a validated science, and there is clear evidence that higher quality prevents incident cancer and cancer death. Quality must be addressed at the levels of the system, provider, and individuals, to maximize the benefits of screening for any population. We review the important aspects of measuring and improving the quality of colorectal cancer screening.

Keywords: colonoscopy; fecal immunochemical test; Colorectal cancer; colorectal polyp

Evidence-based quality assurance guidelines that cover the entire screening process and provide a list of key performance indicators and standards have been published by the European Union (EU) commission.[1] Comprehensive documents that addressed colonoscopy quality were issued by the United States (US) Multi Society Task Force (MSTF) [2], by a special task force on quality [3, 4], and recently by the European Society for Gastrointestinal Endoscopy (ESGE). [5] Quality indicators for fecal immunochemical test (FIT) performance and follow up were also issued.[6] A detailed evaluation of colonoscopy quality parameters is not feasible; we propose priorities for quality measurement in colorectal cancer (CRC) prevention and discuss proven methods to optimize these quality indicators.

Several tests are available for CRC screening, but the most common options are FIT, colonoscopy, and sigmoidoscopy. Figure 1 lists proposed priority CRC screening quality measures for a healthcare delivery system. These measures relate to CRC screening adherence, colonoscopy (the primary screening method and preferred test for diagnostic analysis and post-polypectomy surveillance), and FIT. We discuss measures to evaluate CRC screening quality and methods to optimize these quality indicators.



**Maximizing Adherence to Screening and Diagnostic Colonoscopy Evaluations**

Screening programs have reduced CRC incidence, mortality, and surgery at the population level,[7-9] but screening rates remain low in several countries. Screening rates are consistently low, independent of ethnicity and educational level, among the uninsured, individuals of low socioeconomic status, and individuals with limited access to primary care.[10-13] Non-adherence to recommended protocols is an important attributable factor of CRC burden[13] and the social gradient in screening uptake might increase disparities in mortality[14]. EU guidelines proposed acceptable and desirable adherence rates to CRC screening at greater than 45% and greater than 65%, respectively, and compliance with colonoscopy referral among persons undergoing

screening with a positive result from a primary screening test at above 90%.[1] The National CRC Round Table[15] proposed a 80% adherence target for primary screening and the US Multi-Society Task Force on CRC US set a target of 80% compliance with colonoscopy referral in patients with a positive result from a FIT [6].

*CRC awareness*

Awareness of cancer, as well as of screening modalities, is an important factor in the decision to participate in CRC screening, in that it affects beliefs, attitudes, and motivation.[16] Addressing structural barriers at the health system and organization level might be required to increase participation rates, once awareness has been raised. Analyses of barriers to screening[16] found a link between awareness and health system factors, such as public education and primary care physician efforts, and indicated that although individual knowledge and perceptions drive intentions to participate, issues related to practice organization are important to translate intention into action.[17]

Therefore, the health system, and the context within which it is embedded, affects provider delivery and patient use of screening [18, 19] and compliance with cancer screening recommendations requires multifaceted interactions among patients, providers, and health organizations. Interventions that target multiple levels of care and consider factors outside the individual control of clinicians and integrate different strategies could be the most effective approach to increase uptake of CRC screening.

*System-level interventions*

Evidence for higher uptake rates and reduced coverage disparities regardless of socio-economic status indicates that population-based organized programs, delivered at the national

level or by healthcare systems, can integrate interventions that address health system and individual-level barriers and help establish an organizational framework that gives each eligible subject a chance to participate.[20] Organized programs produce higher rates of uptake, screening, and follow-up assessment than opportunistic screening. In the US, an organized program based on FIT screening achieved 83% adherence in a large healthcare system, [20] whereas national measures of screening, which largely reflect the opportunistic setting in the US, have been stagnant in recent years at approximately 60%.[21]

Higher screening rates and reduced coverage disparities by socioeconomic status have been reported in the EU, in areas where organized programs had been introduced, compared with areas where only opportunistic screening was available.[20] System-level measures adopted within organized programs are establishing a suitable context to maximize the effects of interventions, targeting provider- and individual-related factors by reducing external barriers to the implementation of their decision to engage in screening.

*Financial barriers*

The type of insurance coverage and the cost of the test affect rates of screening and subjects' preferences for specific tests. The introduction of free programs (funded by national or regional governments) and mandatory insurance coverage or elimination of cost sharing for screening and assessment tests, have increased the use of screening. Eliminating these economic barriers resulted in substantial increase (ranging from 7% to 50%, depending on background rates of use) in population coverage, in particular among the low-income, least-educated subjects [22-25].

*Active invitations*

Mailing personal invitation letters, at the recommended intervals, to all eligible subjects, or sending electronic invitations, is a widely adopted, highly effective, organizational measure to engage the target population. This approach is associated with screening uptake, irrespective of the test adopted (Figure 2).[26] Cost-effectiveness is generally lower for client-directed interventions, such as face to face counseling, telephone reminders, or navigators, than for strategies that involve mail or electronic invitations or alerts. Lower cost-effectiveness reduces the sustainability and feasibility of those interventions in the context of large population-based programs.[27, 28] However, direct invitation by primary care physician (PCP) is still a valid option, especially in settings with inadequate information technology infrastructure or limited use of mail or electronic reminders. The combined FIT and multi target stool DNA test is less cost effective than annual FIT, but use of a telephone based navigation system resulted in 71% test completion in a Medicare population.[29]

*Type of screening test*

Multiple tests have been validated for CRC screening. These differ in effectiveness, acceptability, safety, and cost profile. Dislike of specific tests appears to be a barrier to CRC screening, so choice of the screening method provides an additional system-level factor that affects uptake. Introduction of the FIT was associated with an absolute increase in participation (increases ranging from 5% to 16%) in population-based programs [27], compared with the guaiac fecal occult blood test, likely related to the simpler testing procedure. Participation tends to be lower for invasive, endoscopic evaluations (absolute decrease in participation in a single round ranging from 2% to 30% for the FIT vs computed tomography colonography [CTC] and from 5% to 36% for FIT vs colonoscopy).[27,30] Colonoscopy and sigmoidoscopy have the advantage that they bring a patient into compliance for long time

(more than 10—15 years when no neoplasia is detected), whereas adherence to repeated guaiac fecal occult blood tests or FITs decrease rapidly.[31]

There are also sex differences in uptake of FIT vs endoscopy. Women have higher rates of participation when invited for a FIT (absolute difference between women vs men ranges from 2% to 10%), whereas men have higher rates of response to invitations for endoscopy (absolute difference for men vs women ranges from 2% to 5%). Screening uptake did not increase when individuals were offered a choice of tests, compared with an invitation for a specific test.[27]

*Individuals*

High-quality evidence indicates that adoption of strategies to facilitate access to a recommended test,[27] or reinforcement of motivation of subjects to attend,[32] can increase subjects' response to an invitation and affect individual-related barriers (Figure 2). Although studies assessing the specific contribution to screening uptake after distribution of information leaflets, in addition to an invitation letter, had inconsistent results[33], the provision of educational material supports efforts aimed to promote informed participation. [34, 35] Leaflets can also provide information that is tailored to address barriers experienced by specific sub-groups.

Information material, designed to overcome language, literacy, or cultural barriers and developed based on theoretical models of behavioral change, mailed together with the invitation letter, as well as increased reminders, can increase overall uptake [36, 37] at a low cost. The observed absolute increase in uptake varied, ranging from 1% to 20%. In the study reporting the lowest effect, the intervention showed, however, a stronger effect in most

deprived groups, indicating that it might reduce the socioeconomic gradient in screening participation.[36]

*Primary care physicians*

Reports of PCPs demonstrated that provider's involvement can improve compliance to primary screening invitations and recommendations for diagnostic evaluation[38, 39], particularly for less-educated, or older people, who are less likely to use written information material.[40] Changes in practice organization that aim to reduce the effects of commonly reported barriers related to lack of time and resources for preventive care are effective measures to maximize the effects of providers' efforts (Figure 2).

Educational interventions that aim to foster knowledge of program effectiveness, of the accuracy of the adopted method, and of the recommended screening procedures,[41] as well as those that provide regular feedback about individual PCPs' screening rates and their relative performance,[42] can reinforce providers' commitment to promotion of screening. Increasingly, practitioners are evaluated by their success in reaching adherence targets in the opportunistic setting, using available data from electronic medical records.

*Diagnostic colonoscopy after a positive result from a screening test*

Although adherence to primary screening is an important determinant of the magnitude of the health effects of screening at the population level, the expected reduction of CRC burden can be only achieved if subjects with abnormal findings receive timely and appropriate follow up and treatment, if needed. However, although targets of at least 80% have been proposed, many persons who have positive results from screening tests (ranging from 8% to 34%, according to several reports) do not undergo the recommended assessment.[13] Timeliness of

the follow-up examination is also important; 1 study showed that delays of greater than 10 months for colonoscopies (compared with 8–30 days) were associated with a 2-fold increase in advanced stage cancer.[43]

The lack of an established organizational infrastructure allowing for monitoring compliance with the recommended assessments, as well as difficulties in sharing data between clinical and screening services, have been reported as specific barriers to effective follow up of persons with positive results from screening.[44] Economic (cost of the test and/or co-payment), organizational (limited endoscopic resources), and cultural (fear of the test and of cancer, fatalistic attitude) barriers, already documented for primary screening[44] contribute to limit the response to colonoscopy referral following a positive results from screening tests.

System-level interventions, including elimination of financial barriers for further investigations, and implementation of an active recall and fail-safe system, ensuring systematic assessment of all non-responders, were associated with an increase in the proportion of screen-positive individuals who received timely follow up.[45] Providing tailored written information material, offering access to telephone or face to face counselling, addressing fears related to abnormal findings, patient-level navigation, and provider reminders increased compliance with colonoscopy referral, maintaining a high cost-effectiveness ratio also within organized programs.[45]

**Optimizing Colonoscopy Quality**

Colonoscopy is recommended as a primary screening method and it is a preferred diagnostic method for persons with positive results from other methods, as well as for surveillance following polypectomy. For this reason, quality of colonoscopy is crucial to achieve the

expected benefit of screening, independent of the strategy adopted for primary screening. Therefore, it is important to discuss each key performance indicator of colonoscopy in detail.

*How to optimize bowel preparation for colonoscopy?*

The effects of inadequate bowel preparations on colonoscopy resources and costs are substantial [46]. In addition, bowel preparation interacts with detection targets. Inadequate preparation therefore impairs detection and creates inefficiency [47, 48]. In the US, the MSTF recommended that at least 85% of outpatient colonoscopies achieve adequate preparation [49], and the ESGE recommended 90% [50]. Adequate preparation is best defined using clinical grading scales such as the Boston Bowel Preparation Scale, in which a score of 2 or more in each of 3 colonic segments is considered adequate[51]. Excellent and good preparations are also widely accepted as adequate [49]; the MSTF states that a preparation that allowed detection of lesions larger than 5 mm is considered adequate [49]. In scoring rates of adequate preparation, the recommended colonoscopy follow-up interval must meet prevailing surveillance or screening recommendations to be scored in compliance [49].

Over the last decade, the quality of bowel preparation for colonoscopy has greatly improved. Development and widespread implementation of validated bowel preparation scales increased our understanding of variations in quality, set performance standards, and stimulated improvements.[51-53] A true paradigm shift came from delivering the entire dose the day before colonoscopy to split-dose or same-day regimens. This single change increased the rate of adequate bowel preparation from 63% to 85%.[54] There is an inverse correlation between the degree of colon cleanliness and time between the last dose of bowel preparation and the start of colonoscopy.[55] It is now recommended that the last portion of the bowel purgative be ingested 2-5 hours before colonoscopy.[56]

Another milestone was our increased understanding of the importance of oral and written instructions for bowel preparation. Enhanced instructions, consisting of visual aids, social media apps, telephone/short message service (SMS), and smartphone applications, were all proven to optimize bowel preparation[57]. These are now recommended as an adjunct to standard instructions.[56] New low-volume bowel preparations might increase tolerability without compromising the efficacy of cleansing.[56] Although bowel preparation is considered a barrier to CRC screening, lowering the dose of purgative does not seem sufficient to increase colonoscopy adherence rates.[58]

*How to optimize rates of cecal intubation?*

Cecal intubation is defined as the instrument tip passing the ileocecal valve and reaching fully into cecal caput, allowing detailed inspection of the mucosa between the ileocecal valve and appendiceal orifice. The cecal intubation rate (CIR) is a priority measurement—low CIR is associated with interval CRC (iCRC) [59]. Recommended targets include more than 90% for all colonoscopies and more than 95% for screening colonoscopies [4, 5]. Programs should audit the quality of documentation, including naming and photography of cecal landmarks—most importantly the appendiceal orifice [4].

Competence in cecal intubation is usually achieved in the process of colonoscopy training since it is a key measure of skills acquisition.[60] Nevertheless, in routine clinical practice, it is common for CIRs of individual endoscopists or practices to fall below the recommended standards.[61-63] The first step in the process to optimize CIR is to measure and provide feedback on performance.[64, 65] Quarterly report cards were shown to improve CIRs among experienced endoscopists.[66] Other specific improvement interventions include optimization of

bowel preparation,[64] provision of sedation,[67, 68] use of adjuvant magnetic endoscopic imaging[69], and additional training using novel competency assessment tools.[70, 71] An unresolved issue is whether continuous long-term measurement of CIR for colonoscopists who repeatedly demonstrate performance well above thresholds is productive—CIRs of individual colonoscopists are typically stable or increase over time.

*How to optimize lesion detection?*

The adenoma detection rate (ADR) was proposed as a quality indicator for colonoscopy in 2002 by the MSTF. It is generally defined as the percentage of patients undergoing first-time primary screening colonoscopy who are 50 years or older and have 1 or more conventional adenomas detected [3, 4]. The original definition did not restrict measurement to screening [2], though recommended targets were based on screening studies. Recent studies have raised questions about the screening restriction, because screening ADR is intermediate between surveillance ADR (higher) and diagnostic examinations (which are lower, except for those performed for positive fecal blood tests) [72, 73]. Recommendations for ADR include minimum acceptable thresholds, which were recently increased for primary screening in the US to 30% in men and 20% in women, [4] or 25% in mixed population, by the ESGE[52] . Targets for individuals with a positive result from a FIT should be 15%–20% higher than for a primary screening population; these were recommended to be 45% for men and 35% for women by the MSTF[6] . Adjustments based on patient population features such as better general health, obesity, cigarette smoking, etc, are unnecessary [74].

The ADR target is not recommended to include sessile serrated lesions (SSLs, also called sessile serrated polyps and sessile serrated adenomas). The rationale is the well-documented interobserver variation between pathologists in differentiation of SSLs from hyperplastic

polyps (HPs). In a recent clinical trial, ADR included both conventional adenomas and SSL [75], but all lesions detected were reviewed by central expert pathologists. A separate detection target for SSLs has generated some interest, and could be implemented at the institutional level [76, 77]. One solution to the problem of differentiating SSLs from HPs is to create a SSL plus HP target. However, this target requires confining the measurement to proximal colon to avoid incentivizing removal of diminutive HPs from the rectosigmoid. Intra- and inter-observer variations among colonoscopists in identifying landmarks such as the splenic flexure and sigmoid descending colon junction make prospective accurate application of a target confined to the proximal colon unreliable. In general, the correlation between detection of conventional adenomas and various serrated detection targets has been high [77-83]. Given the challenges of a separate serrated detection target, this correlation indicates that a continued focus on ADR in quality programs is reasonable.

Although ADR is not an ideal quality parameter, it has been widely validated by studies reporting its association with iCRC[84] and fatal iCRC.[85] Alternative proposed measures, such as iCRC rates, adenoma and advanced adenoma miss rates, advanced adenoma detection rate, adenomas per colonoscopy, and polyp detection rate all have deficiencies, including issues such as lack of feasibility, requirement for tandem studies, a tendency to measure pathologist performance rather than endoscopist performance, or susceptibility to gaming when used prospectively.

The benchmark of adenomas per colonoscopy (APC) [86] provides greater separation among endoscopists than the ADR[87, 88] and avoids the theoretical concern about 1 and done (in which an endoscopist detects 1 adenoma and then performs a suboptimal examination of the remaining colon).[89] Generally, ADR and APC correlate [87, 88]. In the long term, converting

from ADR to APC appears to be advantageous, because APC measures the quality of colonoscopy over the complete examination, provided that APC is validated as a predictor of iCRC. Implementation of APC should be accompanied by agreement on handling procedures for multiple small and diminutive adenomas in the same colon section—placing them in separate containers for pathology examination would increase costs. Photography of multiple lesions to document the number of lesions, accompanied by the current practice of placing lesions of the same predicted histologic type and from the same segment of the colon in 1 bottle, is could reduce the pathology costs with APC[90]. Regardless of using photography to assist in documentation of APC, routine photography of advanced lesions, including photographs before and after resection, is widely considered best documentation practice.

Increases in ADR have been associated with reduced risk of iCRC and fatal iCRC.[91, 65] Therefore minimum thresholds should activate remediation when not reached [4]. Colonoscopists with ADRs above recommended thresholds should also strive to improve their ADR,[92] since CRC protection increases with ADRs above minimum thresholds. Although the target thresholds are unknown, colonoscopists could be reasonably recommended to aspire to ADRs of 40%–50% in primary screening[92]—the risk of iCRC continued to decrease to these levels of ADR.[85] Remediation of low detectors requires multifaceted change of endoscopists behavior and examination technique, which can be coupled with improved imaging technology.[93-95] Audit and performance-enhancing feedback seem have the greatest effect in improving ADR,[91, 96, 97] although not all programs have proven successful.[98] The optimal frequency and method of providing feedback are unknown. A major focus should be put on examination technique, which could be deconstructed into 4 main components: looking behind all folds, cleaning residual stool, providing adequate bowel distension and withdrawing slow enough.[99]

Effective interventions to improve fold examination include double inspection of the right colon (either forward viewing or in retroflex)[100] and use of mucosal exposure devices (Endocuff, Endorings, or G-Eye balloon). Of all mucosal exposure devices, the Endocuff is the most comprehensively studied and has the best evidence of efficacy.[101, 102] Better cleaning of residual stool can be achieved by optimized cleansing regimens described earlier in this article or use of water exchange method.[103] Successful bowel distension can be achieved by dynamic position changes during withdrawal.[104] Application of effective examination techniques will consistently result in longer withdrawal times. Withdrawal time was originally recommended to average 6–10 minutes in normal colonoscopies, and then altered to 6 or more minutes.[105] Detection of adenomas[92] and probably also serrated lesions[106] is optimized at a mean withdrawal time of 9 minutes. Short withdrawal times are a surrogate of poor examination technique, and indicate need for technique remediation for endoscopists with low ADRs. However, a policy of adequate withdrawal time as the primary quality indicator was unsuccessful.[107]

Of the multiple imaging modalities developed to improve ADR, relatively few were proven effective in clinical practice. High-definition white-light imaging increased absolute ADR by 3.5% compared with standard definition endoscopy.[108] However, it might require more than 1 change in instrument generation to increase ADR in practice.[109, 110] Conventional chromoendoscopy increased ADRs by 6-7% compared with standard or high-definition white-light colonoscopy, although chromoendoscopy adds 4–10 minutes to the procedure time and is considered too cumbersome to implement in clinical practice.[111] A change from topical to a per oral multimatrix structure methylene blue formulation was recently reported to increase ADR by 8.5%.[112] Electronic chromoendoscopy was generally considered ineffective,[113] but a

recent meta-analysis showed that brighter-illumination narrow-band imaging increased ADRs, particularly when bowel preparation was excellent.[114] Similarly, Fujinon has developed 2 forms of brighter-illumination electronic chromoendoscopy, called blue-light imaging and linked-color imaging; each increased ADRs in initial studies.[115]

*Optimizing rates of polyp resection*

Ineffective resection of precancerous lesions might contribute to iCRC.[116] Rates of complete resection of lesions 5–20 mm varied 3-fold, [117] along with assessments of polypectomy competency. [118] Two scales have been validated for measuring resection skill.[119, 120] The Direct Observation of Polypectomy Skills applies to small lesions and endoscopic mucosal resection.[119] The Cold Snare Polypectomy Assessment Tool is used specifically for cold snaring[120] and is easily applied to routine colonoscopies. Detailed recommendations on optimal resection technique were made by the ESGE.[52, 121]

Lack of formal national guidelines and training courses in colorectal polypectomy or endoscopic mucosal resection are likely key reasons for high variability in competence and complete resection rates among endoscopists.[118, 122] There is considerable variation and incompetency in polyp assessment, including its size[123] and morphology[124] as well as accuracy in positioning snare over the lesion and grasping an appropriate amount of tissue.[118] Use of structured competency scales (such as the Direct Observation of Polypectomy Skills or Cold Snare Polypectomy Assessment Tool) might improve polypectomy training.[125] Lecture-based training for gastroenterology fellows seems insufficient to increase polypectomy competence.[126] Importantly, feedback and training in polypectomy performance, coupled with educational videos, improve polypectomy skills, especially for diminutive polyps.[127] For polyps larger than 3 mm, emphasis on appropriate resection technique using a snare instead of

biopsy forceps is crucial.[52, 128] For larger lesions, priorities should include training with ex vivo models,[129] appropriate number of procedures,[130] and focus on en bloc resection of all pedunculated and non-pedunculated polyps up to 20 mm.[116] The EU guidelines for quality assurance mandate that all endoscopists performing screening colonoscopies should be level 3 competent in polypectomy, which includes removal of all pedunculated polyps and virtually all nonpedunculated polyps up to 20 mm.[131]

*How can we optimize post-polypectomy surveillance?*

Colonoscopy is overused in low-risk patients [132] and underused in high-risk patients.[133] Recommendations for screening and surveillance intervals should be monitored for consistency with published recommendations.[134, 135] Adherence to post-polypectomy surveillance is low, with more than 50% of patients undergoing surveillance either too early or too late.[136] The key to optimizing surveillance is to ensure that correct recommendations are given by gastroenterologists, surgeons, or family physicians, because these are the most important predictors of patient adherence.[137, 138] Another solution is to integrate surveillance interval into electronic medical record system (to set reminders), so other provides can follow patients and refer them at proper intervals.[139]

**How Can We Optimize Screening Sigmoidoscopy?**

There is evidence that single sigmoidoscopy screens can reduce CRC incidence and mortality. However, data do not show an additional benefit of subsequent rounds of screening.[140] There are many parallels in developing and monitoring quality assurance in sigmoidoscopy programs to colonoscopy-based programs. Just like colonoscopy, there is high-quality evidence for wide variations in sigmoidoscopy performance[141, 142], which translate into differences in cancer prevention[143]. Important quality metrics for sigmoidoscopy include prep

quality, depth of insertion, and polyp detection. Recent studies reported the association of withdrawal times of at least 3.25 minutes and scope advancement to the splenic flexure with increased adenoma detection[144]. Guidance regarding quality performance in sigmoidoscopy have been provided by some organizations[145, 146].

**How Can We Optimize the FIT?**

There are important considerations for implementing high-quality FIT-based programs. For example, decisions must be made about the type of FIT (such as qualitative vs quantitative) to be used and the frequency with which it will be applied. Separately, decisions must be made about which FIT brand to use—if a quantitative platform is used, the numeric definition of a positive result must be established. Fortunately, there have been many articles published on these topics. Several large-scale national programs and clinical trials have produced findings that can be used in considering development of high-quality FIT based programs (see Table 1).

*Optimizing patient preparation for the FIT*

Adherence increases the success of any CRC screening program, so programs should aim to simplify regular completion of FIT. A significant advantage of the FIT, compared with the guaiac fecal occult blood test, is that the FIT directly measures hemoglobin in stool, and results are not affected by diet [147]. So, to maximize adherence, no dietary changes should be recommended before stool collection. Similarly, simplifying recommendations about medications (such as aspirin and non-steroidal anti-inflammatory drugs [NSAID]) is also important. Hemoglobin degrades during gastrointestinal transit, so drugs that cause upper gastrointestinal tract bleeding should not greatly affect FIT results. Two recent meta-analyses found that NSAIDs and anticoagulants have little to no effect on test characteristics[148, 149] and

support US multi-society task force recommendations not to stop taking NSAIDS before a FIT[6]. Direct-acting oral anticoagulants might reduce the positive predictive value of FIT to a significantly greater degree than conventional anticoagulants[150], but further studies are needed.

*Optimizing choice of FIT and application*

There are qualitative and quantitative FITs. Qualitative tests have a visual indicator that indicates when there is hemoglobin in the sample, above a pre-set level. Quantitative tests rely on immunoturbidimetric methods and automated readings, in which the cut-off value for a positive result can be set by the operator[151]. Quantitative tests have a number of advantages over qualitative tests; large national programs and clinical trials therefore often use the quantitative tests. There is evidence for significant variation in performance of qualitative tests[152], and quantitative tests allow better matching of definitions of positive results to colonoscopy resources. For example, a screen program in The Netherlands changed a positive cut-off value from 15 to 47 ug Hb/g feces to improve positive predictive value and decrease colonoscopy burden[153]. However, in countries where colonoscopy resources are less limited, quantitative tests can facilitate application of the test to increase sensitivity. In fact, in an analysis of 16 studies, a FIT threshold of 10 ugHB/g identified patients with colorectal cancer with 91% sensitivity and 90% sensitivity.[154]

It is also important to determine how many FIT samples (1, 2, or 3) will be tested. Lower number of samples per cycle increase adherence. For example, in randomized controlled trials that compared results of FITs to 3-card conventional fecal occult blood tests, participation was more than 20% higher in the FIT group [155]. In a recent population-based study over 4 rounds that directly compared 1 FIT vs 2 FITs (on a biennial schedule), there was no

significant increase in diagnostic yield or decrease in interval CRC between the groups. Colonoscopy demand was higher in the 2-FIT group and the authors concluded that the 1-sample FIT was the preferred approach.[156]

A separate issue is whether to perform FITs on an annual or biennial basis. Although annual screening, most population-based programs outside the US and 2 other trials of FIT vs colonoscopy used biennial testing (see Table 1).[157]Tradeoffs between the approaches include increased participant burden with more frequent application and delays in diagnosis of important lesions (such as advanced adenoma) with less frequent application. Differences in important outcomes including the overall number of positive results and detection of advanced neoplasia were not large, and programs have latitude in choosing the optimal approach within a population.[158]

*Optimizing FIT distribution and quality control*

Recent studies[159-161] confirmed findings from earlier studies[162-164] that positive results of FIT testing decrease in warmer months and might affect lesion detection. Programs are not currently considering season in FIT distribution, but do emphasize the importance of returning samples quickly. Improved FIT buffers are being developed, to prevent sample degradation.[165] Quality control within the laboratory, including standardized result reporting, is required for program success.[166, 167] Although the details are outside the scope of this review, a quality control program in The Netherlands investigated how changing collection devices, reagents, and laboratories affects positive results [168]. FIT-based screening programs should track the percentage of kits received that cannot be processed; in the US, this value is recommended to be below 5%.[6] Quality improvement efforts have been effective in reducing rates of laboratory-rejected samples.[169] For example, placing red stickers on the FIT to

remind users of the need for rapid return increased rates of sample processing at the laboratory.

**New Screening Strategies Under Evaluation**

CTC is recommended for patients with positive results from a screening test who have contraindications to colonoscopy. The role of CTC as primary screening test is still under evaluation. Guidance for CTC quality has been published.[170, 171] Although the details of those recommendations are beyond the scope of this review, some general statements can be made. High-quality colonic preparation, often with fecal tagging and adequate insufflation, is important for adequate test performance.

With regard to imaging, use of multi-detector scanners is key, along with efforts to minimize radiation exposure. Although recommendations about primary mode of reading are generally not specific (such as starting with either the 2-dimensional or 3-dimensional rendering), it is clear that software should provide multiple display formats. Reporting should be standardized—the CT Colonography Reporting and Data System [170] is generally used for this purpose. Finally, it is important to use a data registry to track performance. The ability to regularly audit patient safety and outcome for use CTC is key, and performance indicators have been described.[171, 172]

*Multi-target DNA test*

MT-DNA test is available for only routine screening in the US. The Food and Drug Administration approved this proprietary device (Cologuard; Exact Sciences, Madison WI) in 2014 and the Center For Medicare and Medicaid Services provided payment coverage at a frequency of every 3 years.[173] After an order is placed, the company directs the subsequent

distribution, receipt, processing, and results notification. Details regarding the laboratory methods and analytic use of the results have been described.[174] In brief, institutions or programs using this device would rely on the Exact Sciences laboratory for all quality control.

**Future Directions**

CRC screening reduces cancer-specific mortality and incidence. The effectiveness of cancer screening, however, relies not only on the efficacy of screening test but also on the process of screening delivery, which includes adherence, quality of screening, and analysis of results. This complicated process requires monitoring and optimization of several steps. Screening programs create a perfect framework for comparative effectiveness research, in which screening optimization strategies can be tested. This framework includes joint database management systems, resources already allocated to potential interventions, and large numbers of potential participants.[175, 176] Several aspects of CRC screening quality, such as rates of colonoscopy completion or adenoma detection, or adequacy of bowel cleansing, have been addressed. Others, such as variable and insufficient rates of adherence to screening, rates of complete endoscopic resection, and adequate post-polypectomy surveillance, are important quality issues to be tackled in the near future.

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Figure legends

Figure 1. Summary of CRC screening quality measures and key optimization strategies.
Figure 2. Solutions and interventions to optimize CRC screening adherence

Table 1. **Application of FIT in Trials and National Screening Programs**

| **Program or Study** | **Target age** | **Frequency** | **Number of FITs per cycle** | **FIT type** | **Brand** | **Threshold** |
|---|---|---|---|---|---|---|
| ColonPrev RCT (Spain) | 50–69 | biennial | single | quantitative | OC sensor | 15 ug Hb/g feces |
| Screesco randomized controlled trial (Sweden) | 59–62 years old | biennial | single | quantitative | OC sensor | 10 ug Hb/g feces |
| CONFIRM RCT (US) | 50–75 | annual | single | quantitative | OC sensor | 20 ug Hb/g feces |
| Denmark National Screening Program | 50–74 | biennial | single | quantitative | OC sensor | 20 ug Hb/g feces |
| Dutch National Screening Program | 55–75 year old | biennial/ | single | quantitative | FOB-gold | 47 ug Hb/g feces |
| Italy National Screening Program | 50–74 years old | biennial | single | quantitative | OC-hemodia | 20 ug Hb/g feces |
| National Cancer Screening Program of Korea | 50 years or older | annual | single | quantitative | OC-sensor | 20 ug Hb/g feces |
| Taiwanese National Screening Program | 50–75 year old | biennial | single | quantitative | OC-sensor and HM-Jack | 20 ug Hb/g feces |
| US/Kaiser Permanente | 51–75 year old | annual | single | quantitative | OC sensor | 20 ug Hb/g feces |