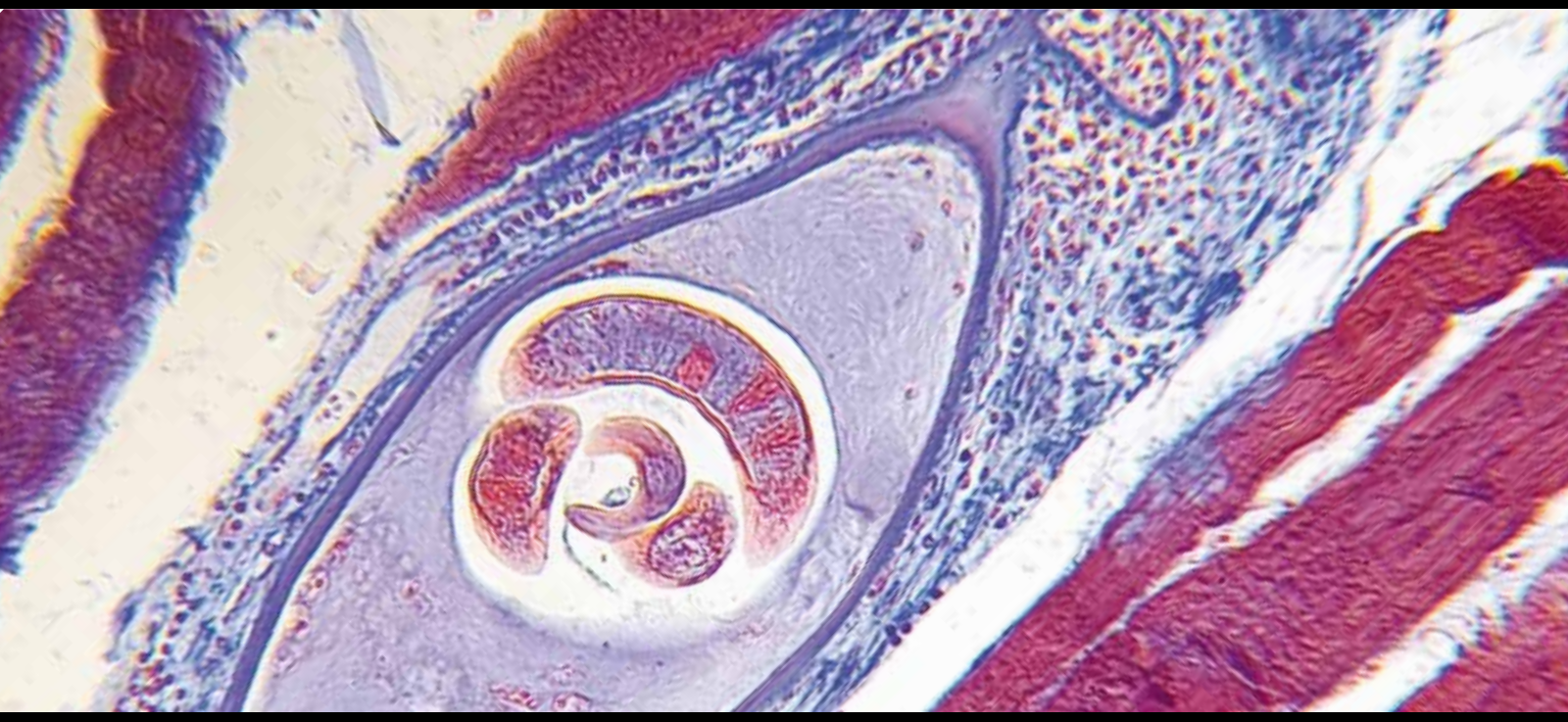
Gastroenterology Research and Practice

Colorectal Cancer Screening

Guest Editors: Enrique Quintero, Yutaka Saito,
Cessare Hassan, and Carlo Senore



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Editorial Board

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Editorial

Colorectal Cancer Screening

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Colorectal cancer (CRC) is the most common malignancy worldwide if men and women are considered together, with more than 1,200,000 new cases per year. The highest incidence rates are found in Australia and New Zealand, Europe, and North America. In addition, it represents, after lung cancer, the second leading cause of cancer-related death among these populations.

CRC can be preventable as more than 85% of tumors arise in a premalignant polyp. Therefore, the aim of CRC screening is to reduce mortality by identifying individuals with pre-symptomatic neoplastic lesions who may require further examination and treatment. Screening tests should be workable, unexpensive, acceptable, sensitive, specific, and safe. However, none of the available recommended tests for CRC screening fulfill these premises. At present, the most acceptable strategies for screening in the average-risk population (individuals without a family history of CRC between 50 and 74 years) are fecal occult blood test (FOBT) every year or biannually, sigmoidoscopy every 5 years, and colonoscopy every 10 years. Other provocative procedures such us computed tomography colonography, faecal DNA analysis, and other molecular tests have emerged as an alternative method during the last decade and are actually under evaluation. By contrast, in individuals with familial risk (first-degree relatives of patients with CRC), colonoscopy is empirically recommended from age 40 or 10 years before the age of diagnosis of the youngest relative.

Compliance is one of the main factors influencing the success of any population-based screening program. If the test is too complicated to perform or not easily accepted by the target population, the participation rate will be poor and the effectiveness of the program will be low. In fact, this is a relevant drawback in many CRC screening programs running worldwide, with compliance rates between 25% and 67%.

In the current special issue, worldwide experts address several controversial aspects related to CRC screening in average-risk population. There are two papers analyzing the main barriers and interventions that may determine screening uptake. A. Z. Gimeno García reviews the factors related to CRC screening behavior and the interventions that may improve screening uptake, whereas G. G. Medina et al. are reporting the results of a survey that explores the main barriers experienced by screeners and nonscreeners. In addition, the effectiveness of molecular fecal testing and the applicability of image-enhanced endoscopy to improve early detection of colorectal neoplasms is approached in three additional papers. R. Kanthan et al. analyze the genetic and epigenetic fecal molecular markers that are being implemented for the identification of malignant and premalignant colorectal lesions; H. Aihara and H. Tajiri reviewed the advantages and limitations of autofluorescence endoscopy for CRC screening, suggesting this technique as a potential tool for improving CRC-related mortality in the forthcoming years; N. Tamai and coworkers actually show the benefit of autofluorescence imaging over narrow-binding image, chromoendoscopy with indigo carmine, and white-light endoscopy, for detecting laterally spreading colorectal tumors. Moreover, M. Sekiguchi et al. compare cost effectiveness of one-time colonoscopy screening versus biennial fecal

immunochemical testing in a retrospective study carried out in Japan. They conclude that colonoscopy is a cost-effective screening strategy in the Japanese average-risk population. Finally, C. Senore, C. Hassan, Y. Saito, and E. Quintero summarize the recent advances regarding strategies for CRC screening, they address the novel implemented endoscopic technologies to improve the detection of nonprotruding neoplasms, and finally they discuss the factors influencing cost effectiveness in the setting of CRC screening.

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Review Article

Progress and Challenges in Colorectal Cancer Screening

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Although faecal and endoscopic tests appear to be effective in reducing colorectal cancer incidence and mortality, further technological and organizational advances are expected to improve the performance and acceptability of these tests. Several attempts to improve endoscopic technology have been made in order to improve the detection rate of neoplasia, especially in the proximal colon. Based on the latest evidence on the long-term efficacy of screening tests, new strategies including endoscopic and faecal modalities have also been proposed in order to improve participation and the diagnostic yield of programmatic screening. Overall, several factors in terms of both efficacy and costs of screening strategies, including the high cost of biological therapy for advanced colorectal cancer, are likely to affect the cost-effectiveness of CRC screening in the future.

1. Introduction

Colorectal cancer (CRC) can be prevented as more than 85% of tumors arise in a premalignant polyp. Therefore, the aim of CRC screening is to reduce mortality and, if possible, the incidence of the disease by identifying individuals with presymptomatic neoplastic lesions who may require further examination and treatment [1].

The most extended CRC screening strategies are based either on annual or biennial fecal occult blood tests, with colonoscopy reserved for patients testing positive, or on endoscopic procedures performed one-time or every 5 years for flexible sigmoidoscopy (FS) or every 10 years in the case of colonoscopy. In addition, other screening procedures, such as CT colonography and fecal DNA analysis, are under current investigation.

Compliance to screening and accuracy of the screening tests are the two major determinants of the effectiveness of a screening program. Although evidence from several studies have shown that some of the above-mentioned strategies are effective [1–4] and cost-effective [5], participation is still poor with compliance rates lower than 50% in population-based programs carried out in Europe and USA. This is a current bone of contention since it has been suggested that new strategies, including either the combination of established tests (i.e., fecal immunochemical test (FIT) and endoscopic procedures) or the implementation of novel screening tests that do not require bowel preparation and do not cause discomfort (i.e., blood biomarkers) might substantially improve the current adherence to CRC screening.

During the last decade there has been a marked improvement in the performance of the screening tests for detecting CRC and preneoplastic lesions. Several randomized controlled trials have shown that the novel semiquantitative fecal immunochemical tests (FITs) are better accepted [6] and have a better performance than the traditional chemical (guaiac) test for detecting colorectal neoplasia [7, 8]. In addition, new technologies (i.e., image-enhanced endoscopy (IEE)) have been introduced to improve endoscopic polyp detection [9], although its influence in the framework of screening still needs to be defined.

CRC screening is not only an effective tool for reducing CRC-related mortality and incidence, but also has been estimated to do so at acceptable costs. Almost ten years ago, the US Preventive Services task force (USPSTF) estimated

that costs per life-year gained of the different screening strategies ranged between 10.000$ and 25.000$. However, several of the screening methods considered today as first-choice screening strategies (i.e., FIT) were not available at the time of the USPSTF report. Recent evidence has confirmed that CRC screening continuous to be cost effective compared to no screening, irrespective of the screening test used. However, cost-effective analysis does not clarify what is the optimal test for CRC screening, because of the uncertainty surrounding many aspects of such interventions.

In this paper, we discuss the possible contribution of the new endoscopic technologies, as a useful tool for screening colonoscopy. In addition, we put in perspective the current strategies for CRC population-based screening and discuss the convenience for combining the established strategies in the near future. Finally, we address the factors that determine cost-effective analysis in the setting of CRC screening.

2. Impact of New Endoscopic Technologies in CRC Prevention

Colonoscopy is considered the gold standard for the detection of neoplastic lesions at risk of progression to CRC and is recommended as a first-line screening test in average and high-risk populations. Its main advantage is that removal of adenomas or early cancer can be performed during the same procedure whereas all other screening tests require colonoscopy for confirmation and removal. However, colonoscopy has also important limitations: first, the risk of major complications (postpolypectomy bleeding and perforation [10] are estimated very low (0.1 and 0.3%, resp.)) for symptomatic patients, but still may be relevant in the framework of screening programs, where asymptomatic subjects are explored; second, although colonoscopy is considered the reference standard for the detection of colonic neoplasia, polyps are still missed. A substantial adenoma miss rate of 20 to 26% for any adenoma and of 2.1% for large adenomas ($\geq$10 mm) was reported in tandem colonoscopy studies [11]. Adenoma detection rate is highly dependent on quality standards including colonoscopist skills, technology, and several patient-related factors [12]. This section reviews the new endoscopic technologies that may significantly reduce the adenoma miss detection rate associated with conventional colonoscopy.

2.1. Wide-Angle Colonoscopy. A prototype wide-angle colonoscope did not eliminate polyp miss rates [13], however, simulation of a colonoscope with a 170-degree field of view resulted in 6% reduction compared with the commonly available 140-degree angle of view of most colonoscopes. The latest generation of wide-angle high-definition colonoscopes improves rates of adenoma detection by 22%, compared with older technology endoscopes used in routine private practice [14].

2.2. The Third Eye Retroscope (TER). The Third Eye Retroscope (TER) (Avantis Medical Systems, Inc, Sunnyvale, CA, USA) is a newly developed imaging device providing a retrograde image of the colon. This device has proved effective in improving polyp detection on the proximal sides of folds in animal models [15] and has also proved safe in humans [16, 17]. Contrarily to wide-angle colonoscopy, TER has the inconvenience of requiring the visualization of dual monitors by one endoscopist and the occupation of the scope's biopsy channel, making difficult its use in routine clinical practice.

2.3. Image-Enhanced Endoscopy (IEE). New image-enhanced endoscopy (IEE) such as narrow band imaging (NBI) system and endoscopic autofluorescence imaging (AFI) system have been developed in order to visualize flat-type colorectal tumor or tumor's surface mucosal or capillary pattern clearly.

2.3.1. Narrow Band Imaging (NBI) System. NBI has been shown to be helpful for early detection of superficial cancer in the head and neck region and the esophagus [18]. In the colorectal region, this modality was expected to enable early detection of adenoma lesions; however, both positive [19, 20] and negative [21–24] results have been reported, and some researchers have concluded no improvement in the adenoma detection rate of NBI compared with white-light colonoscopy (WLC).

One reason for these conflicting findings could be the difference between the optical-electronic technologies employed in videoendoscopes in the NBI systems used sequential system (LUCERA; Olympus Optical Co.) versus nonsequential system (EXERA II; Olympus Optical Co.). Further, differences in the endoscope (low resolution versus high resolution) and imaging (surface structure enhancement and index of hemoglobin color enhancement) settings can influence the detection of the same lesion. Moreover, the colonoscopist's experience may have a considerable impact on the detection rate: if the colonoscopist does not have sufficient training in chromoendoscopy of flat and depressed lesions with an NBI system, the usefulness of NBI for adenoma detection may not be evident. Finally, most of the previous studies used a single-center design.

We reported that the A-5 image setting of the surface structure enhancement function together with the level 3 adaptive index of hemoglobin color enhancement function seem to be the most suitable for detection of colorectal adenomas [25, 26]. To overcome the aforementioned confounding factors, we evaluated the colonic adenoma detection rate of NBI versus WLC by using consistent NBI system, endoscope, and imaging settings in a multicenter randomized trial (RCT) using cross-over design. This RCT was conducted in the right colon for 813 patients using high-definition colonoscopy and NBI settings with surface structure enhancement. This large randomized trial did not show any objective advantage of NBI over WLC in terms of improved neoplastic lesion detection.

2.3.2. Autofluorescence Imaging (AFI) System. AFI produces real-time pseudocolor images to identify gastrointestinal malignancies [27, 28] as well as malignancies of larynx,

cervix, lung, and bladder. During AFI colonoscopy, nonneoplastic lesion appears green, while neoplastic lesion has a magenta (reddish purple) image. The usefulness of AFI for differential diagnosis between neoplastic and nonneoplastic lesions has been reported; however, there is scarce information regarding its effectiveness for colorectal polyp detection in comparison with conventional white-light colonoscopy (WLC). Therefore, the utility of AFI to improve colorectal tumor detection still remains controversial. We therefore conducted a pilot study to evaluate whether AFI can detect more colorectal polyps than WLC. Interestingly, our study showed that AFI system improved the detection of right-sided colonic polyps, especially flat and/or diminutive adenomatous lesions compared to conventional WLC.

In the future, further trials should be performed to validate the usefulness by the combined use of AFI and NBI system for CRC screening.

2.4. Capsule Endoscopy. Colon capsule endoscopy is a new technique to visualize the colon, originating from small bowel imaging. Van Gossum et al. [29] were the first to evaluate the effectiveness in a prospective setting. In high-risk patients, sensitivity and specificity for detecting polyps ≥6 mm were 64 and 84%, respectively, whereas sensitivity and specificity for advanced adenoma detection were 73% and 79%, respectively. The accuracy of the second-generation colon capsule for adenoma detection was promising, with an estimated higher sensitivity and specificity [30]. Compared with full colonoscopy, the accuracy of colon capsule is considerably lower and an even more extensive bowel cleansing is needed. Capsule endoscopy has not yet been evaluated in an average risk screening population.

In summary, total colonoscopy is accepted as the most accurate method of investigation for the large bowel, however, colonoscopy still may miss lesions responsible for cancer development. Several novel devices have been introduced to find flat or depressed tumors or lesions hidden behind folds in the colon. Although some of these emergent technologies such as wide-angle colonoscopy markedly reduce the rate of missed polyps other more sophisticated devices (TER, NBI, and AFI) needs further evaluation.

3. New Strategies for Population-Based CRC Screening

3.1. Technology Innovation for Established Strategies. The adoption of guaiac-fecal occult blood test (g-FOBT) for CRC screening is supported by sound experimental evidence from the US and European trials, which demonstrated that regular screening is associated with a reduction in CRC specific mortality and, in the context of the US study using rehydrated g-FOBT, also with a reduction in CRC incidence. Although this method, adopted by several nation-wide programs in Europe (Finland, UK, and France) can be suitable for population screening, it carries several limitations. Indeed, the test processing and analysis are not automated and therefore they are labor intensive and involve subjective visual reading, while it is not possible to adjust its cutoff for Hb concentration. Also g-FOBT is not specific for human Hb and it showed a low sensitivity for CRC and even more so for advanced adenomas.

Technology developments have been subsequently introduced to overcome some of these limitations. A significant enhancement has been achieved by using antibodies specific to human globin to detect human blood present in feces. As with g-FOBT, the presence of blood in a fecal sample can be used as a marker to detect significant neoplasia in otherwise asymptomatic people. The potential advantages of these alternative fecal tests based on immunochemical technology (FIT) include the possibility of an automated processing and analysis, allowing for the possibility to adjust the cut off of Hb concentration, and the increase in the test specificity for human Hb. The immunochemical technique increases as well the test sensitivity, as it allows to detect smaller blood losses. The disadvantages of FIT methods include sample instability, which impose specific organizational constraints, and the cost of the test. Cost is however highly dependent on local and national market conditions, while the automated testing process with high throughput devices can offset the higher cost of the kit.

Two recent large trials conducted among average risk people showed a higher attendance and detection rate of advanced adenomas and CRC of FIT compared to g-FOBT screening [6, 8]. These trials confirmed the findings of previous comparative studies suggesting the superiority of FIT over g-FOBT [7, 31–35]. Based on this evidence, FIT was recently recommended as the test of choice for population screening in the European Guidelines on quality assurance for CRC screening [36]. The availability of an increasing variety of FIT devices on the market will likely require the adoption of standard and explicit criteria for assessing those device characteristics, including ease of use, sample stability and transport requirements, reproducibility of test results, cost of the kit and of processing, which need to be taken into account when selecting the most appropriate kit for a specific program.

3.2. Endoscopic Screening: New Evidence and Open Issues. Most countries implementing population-based CRC screening programs have adopted g-FOBT and, more recently, FIT. Only a few pilot projects and two population-based programs in Italy adopted FS as a screening option, while colonoscopy was proposed as primary test for opportunistic screening in the USA, Germany, and Poland. New evidence accumulating over the past few years lead to a change of this scenario, both in terms of evidence and of available strategies.

3.2.1. Sigmoidoscopy. Evidence for endoscopic screening was based, until last year, on observational studies, showing a reduction of the risk of CRC or of CRC-related death among people undergoing endoscopy, or on trials comparing sigmoidoscopy with g-FOBT or FIT, showing a substantially higher yield of neoplasia of a single FS examination as compared to a single round of g-FOBT or FIT screening. The findings of the sigmoidoscopy screening trials presenting

long-term follow-up results [2, 37] consistently indicated that the endoscopic excision of colorectal adenomas is associated with a reduction of CRC incidence and mortality. The estimated incidence reduction in the intention to treat analysis is 23% at 12 years in the UK trial and 18% at 11 years in the SCORE trial; the reduction is higher among people undergoing screening, as shown in the perprotocol analysis, with a 33% and 31% CRC incidence reduction, respectively. Contrary to previous reports [38] suggesting that FS might not be effective among women, the protective effect of FS screening is the same for men as for women in the two trials.

The substantial and long-lasting reduction of CRC incidence, which is still about 80% lower than expected at 10 years in the distal colon, supports the hypothesis of a plateau of the prevalence of distal adenomas [39].

The adoption of a screening strategy based on the offer of the test once in the lifetime seems therefore justified, although the optimal target age range has not been defined yet. In Italy, FS screening is currently offered to subjects aged 58 or 60 [40], targeting a new birth cohort every year, while the UK pilot will target people in the age range 55 to 59. However, no difference in the protective effect of FS screening could be observed in the UK and Italian trials when comparing people younger than 60 to those aged 60 to 64. As long as it might be inefficient, or not feasible, to target all people aged 55 to 64, the issue of defining a specific age range for screening is relevant to the planning of population based interventions. Pooled analyses of the published, as well of the ongoing trials, might be useful to determine if a narrower age range, than the two age classes considered in the main analyses, can be identified.

The reduction of proximal CRC incidence and mortality was low and nonsignificant, ranging between 3% in the UK trial and 15% in the SCORE trial among those who were screened. The observed difference might be related to the higher referral rate for total colonoscopy in the Italian trial, although the estimated additional yield of proximal advanced neoplasia associated with the strategy adopted in the SCORE trial was negligible. The results of the ongoing trials adopting different referral criteria might offer useful information to assess the impact of less restrictive total colonoscopy referral policies on the risk of proximal CRC. The positive impact of high referral rates might be lower than expected, however, as evidence mounts that colonoscopy may not prevent as many cancers in the right colon as in the left.

3.2.2. Colonoscopy. Several observational studies [41–43] demonstrated the overall effectiveness of colonoscopy for reduction of CRC incidence and mortality, but with a marked variance in effectiveness for proximal and distal cancer. A substantial protective effect could be observed for CRC arising in the distal colon, while no effect was observed in the proximal colon. Only one recent case-control study [43] indicated that colonoscopy might represent an effective tool to prevent proximal CRC, although an effect could be observed only among people older than 60. This finding is consistent with the results of the Italian SCORE3 trial [44] comparing FS and colonoscopy, which showed that the detection rate was higher for total colonoscopy screening compared with FS screening only for people aged 60 or older.

It might be related to the known shift to the right of CRCs with age, but the underlying reasons for the observed difference in colonoscopy performance in the proximal and distal colon are still unclear. Uncertainties are related to the role of biological differences that may limit the potential effectiveness of colonoscopy in the proximal colon. The relative frequency of nonpolypoid lesions, which are harder to identify and remove, tends to be higher in the right colonic segments. The predominant genetic pathways of carcinogenesis may differ between left-sided and right-sided cancers, with a higher frequency of serrated neoplasms in the proximal colon. Also, contrary to the trend observed in the distal colon, no evidence of a plateau for the incidence of proximal adenomas has been reported.

The assessment of the protective effect for proximal CRCs achievable with colonoscopy represents therefore the most relevant outcome of RCTs evaluating effectiveness of colonoscopy screening. Comparative studies should be designed to assess whether the magnitude of the incremental benefit of colonoscopy over FS is sufficient to justify the additional risks and costs of colonoscopy for screening in the population. These studies should also shed light on issues concerning the actual implementation of a screening strategy based on colonoscopy, such as the definition of a target age range as well as, eventually, of a screening interval.

3.3. Combined Strategies. Given the limitations of available endoscopy methods, strategies combining FS with FIT represent an option which deserves consideration, as it might ensure an additional benefit over FS alone, in particular for proximal lesions. The potential value of this approach, as a recommended option for CRC screening, is supported by a decision analysis using microsimulation models, included in the latest version of the USPSTF, which showed that a strategy using FS and FIT can have an impact, in terms of life years saved, comparable with that of colonoscopy, assuming a comparable participation to the screening process. Data concerning the actual impact of such strategy are only available from colonoscopy studies estimating the relative contribution of FOBT or FIT and of a surrogate FS. Prospective studies aimed at assessing the performance of such strategy in the context of screening interventions targeting average risk people are lacking. The research question of such studies should be focused on identifying the best way to add FIT to a FS screening program to achieve an increased yield of proximal neoplasms while ensuring high participation rates.

3.4. Promoting Participation while Ensuring High Quality of the Screening Process. The USPSTF CRC screening guidelines pointed out that for all screening modalities the effectiveness of screening decreases substantially as adherence to the regimen declines. They further stated that at the individual level adherence to a screening regimen will be more important in life years gained than the particular screening regimen selected.

Availability of different tests represents indeed a new scenario for mass screening programs, as subject's preferences and attitudes will likely influence the uptake level achievable with different strategies. There is a growing body of literature suggesting that subjects targeted for CRC screening have clear preferences for specific methods, determined by test characteristics. Also, gender, education, and age are associated with the uptake, according to the reports from several studies showing higher response rate among women invited to undergo FIT [6] and a higher attendance rates to FS screening among men and more educated or younger people [6].

The heterogeneity of patient's preferences for how to be screened would therefore support the adoption of strategies favoring their implementation as a possible mean to improve participation in CRC screening, but available evidence for this approach is still limited.

Finally, for screening programs to obtain the optimum result, a high quality of the screening process is needed. Poor quality of the exam has been proposed as one of the possible factors explaining the lack of a protective effect of colonoscopy for proximal CRC. Indeed, inadequate performance of colonoscopy may limit its effectiveness, in particular in the proximal colon, as suggested also by the finding of a higher proportion of interval CRC in the right colon compared to the distal colon. Efforts to improve quality are therefore needed, taking into account that colonoscopy represents not only a potential tool for primary screening, but it is also recommended as a diagnostic tool for people with positive results from different primary screening tests. These same efforts should however be implemented also for all the recommended screening methods. A wide variability in adenoma detection rate has been observed in the context of the trials and programs adopting FS [45–48] and also in the context of FOBT/FIT-based screening quality of laboratory procedures deserves adequate scrutiny.

4. Cost Effectiveness of CRC Screening in the 21st Century

The main purpose of cost-effective models is to provide reasonable estimates on the expected efficacy and convenience of health interventions to the policy makers and, more in general, to the whole society. This in turn may be expected to drive selective implementation of new policies to reduce the burden of any disease in terms of morbidity/mortality and/or treatment-related costs. A further advantage of cost-effective models is to allow a transparent comparison of efficacy and effectiveness among different specialties, in order to allow a productive distribution of economic and financial resources among the different fields. For this reason, the main results of cost-effective models may be expected to be incorporated in clinically orientated guidelines, impacting eventually the clinical field.

Cost effectiveness is critical when applied to health interventions directed to the general population, because of the relevance of both efficacy and cost outcomes. This occurs with breast, cervical, as well as with CRC screening, in which all the population included within a predetermined age cutoff is expected to be invited for the screening intervention. Because of the ethical implications implied in inviting asymptomatic subjects, policy makers may be willing to be reassured about the potential efficacy of a population intervention in terms of risk/benefit ratio. Secondly, because of the large number of people to be screened, generally several millions in each country, policy makers need to be aware of the magnitude of absolute costs to be invested and on the convenience of the intervention.

The main drawbacks of cost-effective models is that, despite the apparent firmness of the cost-effectiveness ratios, cost-effective estimates resound of the underlying uncertainty on the main assumptions postulated when developing the simulation process. Such uncertainty may affect the confidence on any cost-effective outputs, reducing its role in the policy-making process. For this reason, simulation models will never replace clinical estimates on the efficacy of health interventions, such as randomized or controlled clinical studies, which, on the other hand, are absolutely necessary to reduce the degree of uncertainty surrounding cost-effective estimates.

When dealing with CRC screening, cost-effective analysis has consistently shown the favorable profile of CRC screening, irrespectively of the adopted strategy. Such favorable cost-effectiveness, as compared with other medical interventions (i.e., breast cancer screening or renal hemodialysis), appeared to be strictly related with the possibility to prevent not only CRC mortality, but also CRC incidence. Any reduction of CRC incidence will not only nullify the CRC-related mortality, but it will also lead to substantial saving, because of the exclusion of surgery/chemotherapy costs. However, cost-effective simulations did not reach clear conclusions on the optimal test for CRC screening, because of the uncertainty surrounding several aspects of such interventions. Despite less relevant, there is also persistent uncertainty on the optimal age window for CRC screening, as well as on the intervals after negative screening tests or following polypectomy. For this reason, further evolutions in this field may arise from the acquisition of new information on both the efficacy and costs of the different tests recommended for CRC prevention.

4.1. Efficacy. Several sources of uncertainty on the relative efficacy of different CRC screening tests exist in simulation models. First, the natural history of the adenoma-carcinoma sequence has only partially been clarified. For instance, the progression from low- to high-risk polyps, as well as among different size classes (i.e., ≤ 5, 6–9, ≥ 10 mm), is poorly known. Similarly, the information on the progression from large polyps to CRC only relies on one old radiological study at high risk of selective/interpretative bias. The natural history of CRC is also incompletely clarified. Despite the stage-specific survival rates are well documented, the sojourn times among the different stages before the diagnosis have only indirectly been estimated. Finally, the relative rate between CRC arising along the adenoma-carcinoma sequence and *de novo* CRC is still largely unknown. Because

of this uncertainty, models tend to differ on the estimates on the transition rates among the several steps of the CRC cancerogenesis, eventually leading to uncertainty on the superiority of one test over the other. It is self-evident that models in which the adenoma-carcinoma sequence is simulated to be relatively low will favour infrequent, but highly sensitive tests for polyps, such as endoscopy or radiology, whilst models simulating a more accelerated carcinogenesis will favour more frequent CRC-sensitive tests, such as fecal tests. Secondly, there is uncertainty on the long-term efficacy of several screening tests. Such uncertainty mainly depends on the lack of appropriate trials addressing such issue. For instance, there is uncertainty on the long-term efficacies of immunochemical fecal test in preventing both CRC mortality and incidence. Similarly, there is uncertainty on the additional efficacy when repeating such tests more frequently (annual versus biannual). Despite widely used as opportunistic screening test, colonoscopy, differently from sigmoidoscopy, has never been fully validated in randomized trials. Moreover, there are wide discrepancies on the exact rate of CRC prevention with this technique, ranging from 30% to virtually 100%. Thirdly, there is uncertainty on how selective strategies of prepolypectomy filtering may affect the eventual efficacy of noninvasive strategies. For instance, it is unclear whether the selective exclusion of ≤ 5 mm or ≤ 10 mm polyps with CT colonography or capsule endoscopy will sort out in a reduced protection as compared with the endoscopic techniques in which all the polyps are usually removed. Fourthly, when basing simulations on diagnostic rather than population estimates, there is uncertainty on the reproducibility and generalizability of the data. For instance, different immunochemical fecal tests have shown a wide interval of sensitivity values, and, similarly both endoscopic and radiological tests have shown different estimates of accuracy in relation to the study setting.

It is clear that only the progressive acquisition of new and more complete information on all these different aspects related with the efficacy of the tests will allow simulation models to produce a more realistic and valuable comparison among the different tests. For instance, the recent publication of two high-quality trials on sigmoidoscopy substantially reduced the uncertainty on the efficacy of this test on both CRC incidence and mortality, improving the reliability of its modelling. The same will probably applied to colonoscopy, when the final results of the ongoing trials will become available.

4.2. Costs. The main determinants of costs in CRC screening modelling are represented by the procedural costs and the costs related with CRC treatment. Procedural costs will in turn depend on the cost estimate and on the actual exploitation of the different procedures. Despite it is relatively simple to obtain realistic estimates of procedural costs under the Medicare scenario, there is a high degree of variability and lack of transparency among the several US insurances used by <65 year old Americans. Similarly, the reimbursement cost for medical procedures in the public health systems in Europe tends to substantially underestimate the actual exploitation of medical and economic resources, artificially improving the cost-effectiveness profile of CRC screening test. Test specificity is also a major determinant of procedural cost. Consequently, the uncertainty on the exact specificity of fecal tests for advanced adenomas or of radiological procedures for the selected polyp cutoff will generate a huge variability on the final cost-effective estimates. A further cause of uncertainty is related with the application of a financial discounting on the costs occurring in the future years, based on the psychological consideration that money to be spent in the present are considered more valuable as compared to money to be spent in the future. Despite understandable, such assumption will tend to underestimate the absolute burden of costs, potentially advantaging more expensive screening strategies, such as endoscopy or radiology. Thirdly, cost-effectiveness ratio tend to mix between the investments needed in the start-up phase with those required in the following workup of the screening program. However, policy makers tend to provide a higher value to the start-up phase, since the required investments will mainly incur in their running period. This may be one of the reasons for which fecal test-screening program are still favoured in most of the European countries.

In conclusion, we may expect a high degree of evolution from cost-effective models. Such evolution should achieve the difficult task to match the progressive acquisition of clinical information with the actual need and availability of the society. The ultimate aim will be to provide a clear ranking of efficacy and costs of the different choices with a minimal degree of uncertainty on the correctness of these estimates.

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Research Article

Visualization of Laterally Spreading Colorectal Tumors by Using Image-Enhanced Endoscopy

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Laterally spreading tumors may sometimes evade detection by colonoscopy. This study aimed to evaluate the use of image-enhanced endoscopy for visualizing laterally spreading tumors of the nongranular type. We reviewed consecutive patients with 47 non-granular-type laterally spreading tumors that had been examined using white-light imaging, autofluorescence imaging, narrow-band imaging, and chromoendoscopy with indigo carmine. The quality of visualization was evaluated using a 5-point scale by less- and more-experienced endoscopists. Autofluorescence imaging provided significantly better visualization than white-light imaging for both less-experienced and experienced endoscopists. On the other hand, no significant differences were observed between the quality of visualization provided by white-light imaging and narrow-band imaging for less-experienced endoscopists. Autofluorescence imaging provides high-quality visualization of non-granular-type laterally spreading tumors on still images. Multicenter trials should be conducted to confirm the usefulness of autofluorescence imaging in detecting laterally spreading colorectal tumors.

1. Introduction

Colorectal carcinoma is one of the most common cancers worldwide, and its prevalence is steadily increasing in Japan [1]. Colonoscopy is considered the gold standard for the detection of neoplastic lesions at risk of progression to colorectal carcinoma. However, according to the results of back-to-back colonoscopies by Rex et al., the miss rate for adenomas ≥1 cm was 6% [2]. Laterally spreading tumors (LSTs) constitute a subset of nonpolypoidal colonic lesions, which are characterized by lateral and circumferential extension along the colonic wall rather than vertical growth [3]. LSTs are further classified based on their macroscopic appearance. The granular type LST (LST-G) is defined by the presence of aggregates of even or uneven nodules on the surface, whereas the non-granular-type LST (LST-NG) has a smooth surface lacking the granulonodular formations [4, 5]. Owing to the flat shape of LSTs, the miss rate for these tumors might be higher than the 6% reported by Rex et al. In addition, LSTs, particularly the NG type, have a higher potential for malignancy; nearly 30% of LST-NGs are associated with lymph follicular or multifocal submucosal invasion [6]. A reduction in the miss rate for LST-NG could therefore contribute to colorectal cancer prevention. Emerging data suggest that the use of image-enhanced endoscopy (IEE) such as autofluorescence imaging (AFI) and narrow-band imaging (NBI) may lead to improvements in polyp detection rates, although this notion remains controversial [7–15]. In our experience, we have encountered many LST-NG lesions that were better visualized by IEE than by white-light imaging (WL). The aim of this study was to evaluate the quality of visualization of LST-NG provided by IEE.

2. Methods

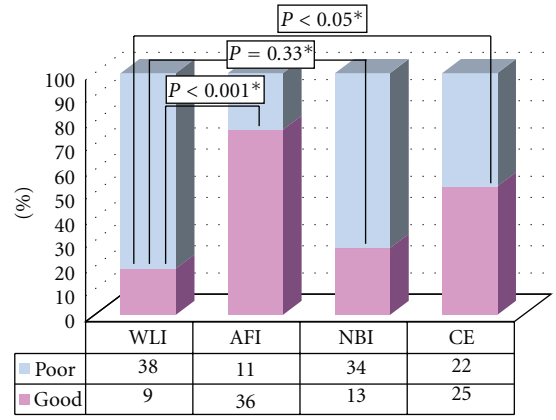
From September 2009 to April 2011, consecutive patients with LST-NG lesions resected by endoscopic submucosal

Table 1: Characteristics of lesions.

Number of lesions	47
Number of patients	45
Sex	
Male	31
Female	24
Age (years)	
Median	69
Range	50–80
Tumor size (mm)	
Median	30
Range	20–60
Tumor location	
Cecum	1
Colon	39
Rectum	7
Histopathology	
Adenoma	5
m-ca	24
sm superficial (sm1*)	11
sm deep (sm2-3)	7

*sm1 : sm < 1000 μm.

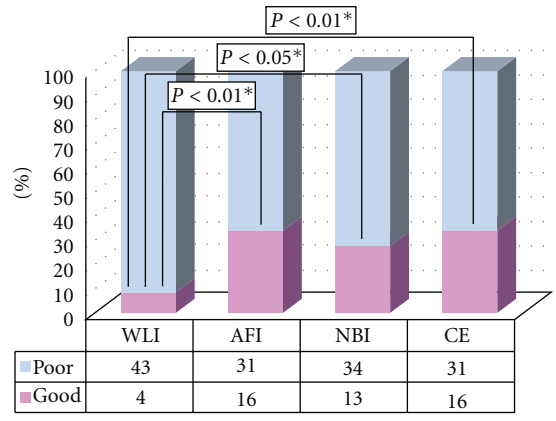
dissection (ESD) in our institution were included in this study. The inclusion criteria for performing ESD on LST-NGs were as follows: (1) evidence of a noninvasive pattern [15–17] and (2) lesions larger than 20 mm that were difficult to resect enbloc by using conventional EMR [18]. First, endoscopic examinations were performed using the white-light mode of the AFI videoendoscope system to identify LST-NG lesions, once lesions were detected, the colonoscopist conducted AFI and NBI examinations by switching first to the AFI mode followed by the NBI mode, and finally lesions were examined by chromoendoscopy (CE) using the white-light mode. AFI colonoscopes (EVIS CF-FH260AZI; Olympus Medical Systems, Tokyo, Japan), light sources (EVIS CLV-260SL; Olympus Medical Systems), and video processors (EVISLUCERA CV-260SL; Olympus Medical Systems) were used in this study. The AFI videoendoscope system is a novel illumination method that produces real-time pseudocolor images. Neoplastic lesions involve a thickening of the mucosal layer and increased hemoglobin so such lesions emit weaker autofluorescence compared to nonneoplastic lesions; therefore nonneoplastic lesion appears green, while neoplastic lesion has a magenta image [7]. The AFI system allowed for immediate switching from WL to AFI and NBI with a button on the control head of the endoscope. CE was performed using 0.4% indigo carmine. Images of the lesions from WL, NBI, AFI, and CE without magnification were captured and electronically archived in the electronic medical records of our hospital. The images were selected by an experienced endoscopist blinded to this study. The WL, NBI, AFI, and CE images for each lesion were downloaded. The images of all the lesions were randomly arranged, and a Microsoft PowerPoint presentation was created. These images did not contain any information to identify the



	WLI	AFI	NBI	CE
Poor	38	11	34	22
Good	9	36	13	25

*Chi-square test

Figure 1: Visualization of LST-NG in group A.



	WLI	AFI	NBI	CE
Poor	43	31	34	31
Good	4	16	13	16

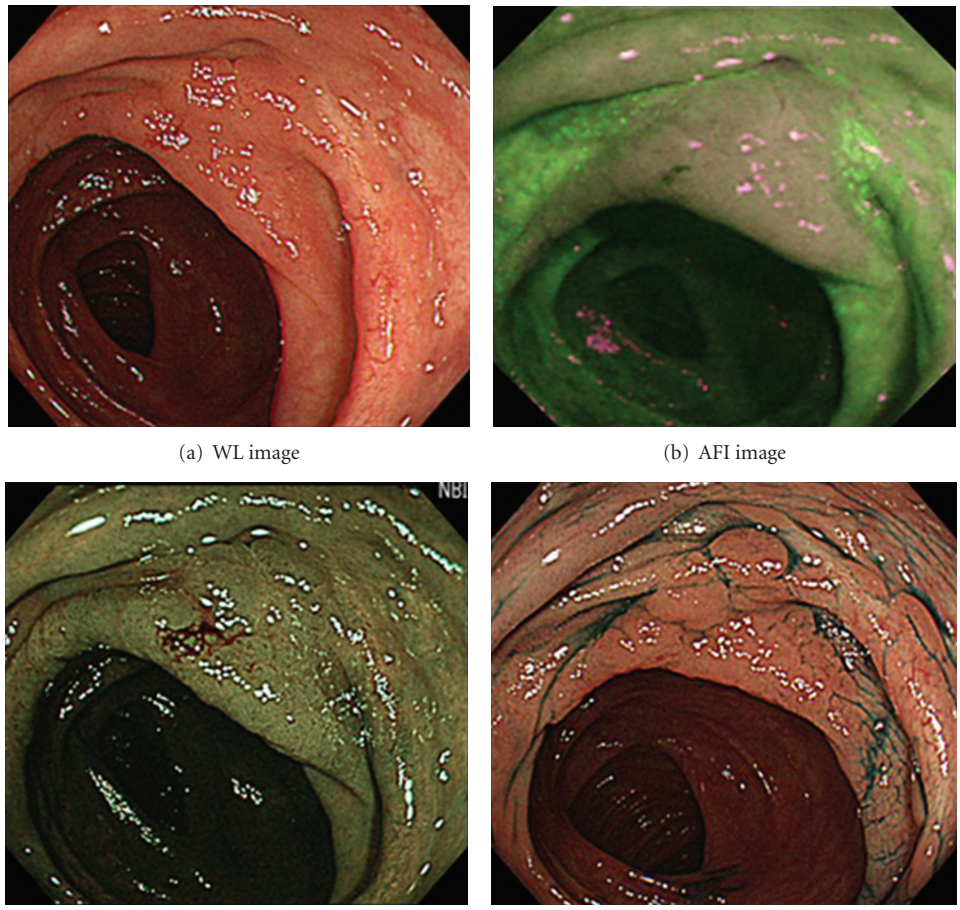
*Fisher's exact test

Figure 2: Visualization of LST-NG in group B.

patient or the lesion. The PowerPoint presentations were sent to the respective raters for their independent evaluation. The images were assessed by 2 groups of endoscopists (A and B). Group A comprised 2 physicians with no previous experience in IEE, and group B comprised 2 endoscopists, each of whom had analyzed over 100 cases by using IEE. Each endoscopic image was assessed and given a global rating for visualization based on the ability to detect the lesion and the clarity of the tumor margins. The images were rated by the endoscopists on a 5-point scale as follows: 5, very well visualized; 4, well visualized; 3, moderately well visualized; 2, poorly visualized; 1, very poorly visualized. The ratings of the images were analyzed separately for groups A and B. For each group of raters, the quality of visualization of lesions that received a score of 4 or more from both the raters was classified as "good". The quality of visualization of lesions with a score below 4 was classified as "poor."

3. Statistical Analysis

Statistical analysis was performed using SPSS for Windows (SPSS, Release 6.0; SPSS Inc., Chicago, Ill, USA, 1993). Statistical significance was defined as a P-value less than 0.05.



(a) WL image (b) AFI image

(c) NBI image (d) chromoendoscopy with indigo carmine

Figure 3: LST-NG lesions categorized as "wellvisualized" using AFI. Location: Transverse colon. Size of the lesion: 45 mm. Macroscopic type: IIa (LST-NG). Pathological findings: well-differentiated adenocarcinoma, low-grade atypia, Pm.

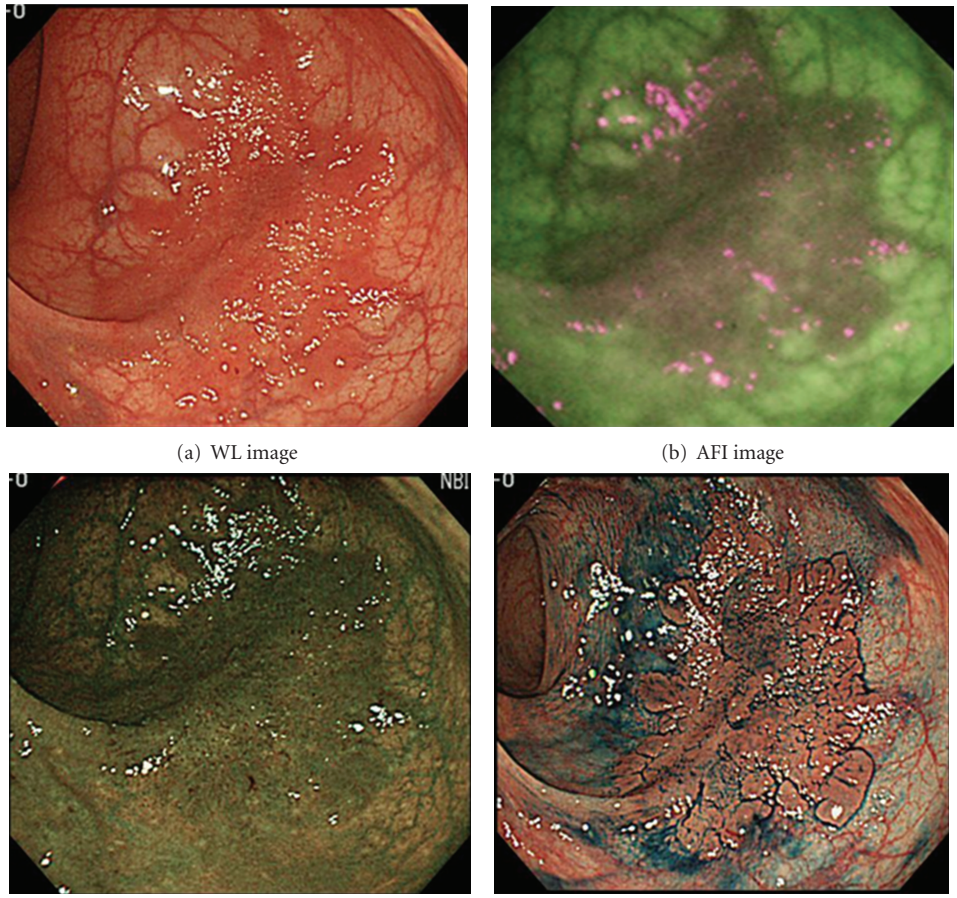
4. Results

In all, 49 LST-NG lesions in 47 patients were included in this study. Two patients with lesions were excluded from this study, because the lesions were not observed in the same field in each of the 4 modalities. Finally, a total of 47 LST-NG lesions in 45 patients were evaluated (Table 1). Of the 47 lesions analyzed in group A, the quality of visualization was categorized as "good" for 6 lesions using AFI, 13 using NBI, and 25 using CE. AFI (36/47) provided significantly better visualization than WL (9/47) ($P < 0.001$). Similarly, there was a significant difference between the quality of visualization using CE (25/47) and WLI (9/47) ($P < 0.05$). There was no significant difference, however, between WLI (9/47) and NBI (25/47) (Figure 1). Regarding AFI visualization, there was no significant difference in the macroscopic subtype, tumor location, or underlying histology between well-visualized and poorly visualized lesions, but well-visualized lesions were larger than the poorly visualized lesions (Table 2).

In group B, the quality of visualization was assessed as "good" for 4 lesions by using WLI, 16 lesions by using AFI, 13 lesions by using NBI, and 16 lesions by using CE. There was a significant difference in the frequency of well-visualized lesions between AFI (16/47) and WLI (4/47) ($P < 0.001$). Similarly, a significant difference in visualization quality was observed between CE (16/47) and WLI (16/47) ($P < 0.01$) and between NBI (13/47) and WLI (4/47) ($P < 0.05$) in group B (Figure 2). Regarding AFI, there was no significant difference in the macroscopic subtype, tumor location, or underlying histology between well-visualized and poorly visualized lesions. Well-visualized lesions were larger than the poorly visualized ones (Table 3).

5. Discussion

Based on the results of our study, AFI provides good-quality visualization of LST-NG lesions, not only for experienced endoscopists but for less-experienced endoscopists as well. The utility of AFI for the detection of colorectal tumors still remains controversial, with studies reporting mixed results [7–9, 15, 19]. In this study, 2 LST-NG lesions were determined to be well visualized by 4 endoscopists (Figures 3 and 4.). As Figures 1 and 2 show, we observed LST-NG lesions that were better visualized using AFI than the other methods. The relationship between visualization and



(a) WL image (b) AFI image

(c) NBI image (d) Chromoendoscopy with indigo carmine

Figure 4: LST-NG lesions categorized as "wellvisualized" by using AFI. Location: lower rectum. Size of the lesion: 45 mm. Macroscopic type: IIa (LST-NG). Pathological findings: well and moderately differentiated adenocarcinoma, pSM (350 um).

detection is uncertain. However, better visualization may enable improved detection of LST lesions, especially those of the NG type, which have been shown to be difficult to detect with CE [4]. It is particularly important to improve the detection rate of LST-NGs, because they are more likely to harbor malignancy; nearly 30% of LSTs of the NG type involve lymph follicular or multifocal submucosal invasion [6]. Though LST-NG lesions are less prevalent than polypoidal lesions, their greater malignant potential necessitates reliable detection methods. This study suggests that AFI is superior to WLI for the detection of LST-NG lesions at least on still images. In the present study, there was no significant difference in the quality of visualization of LST-NGs between WLI and NBI for the less-experienced endoscopists.

We also evaluated LST-G lesions in the same fashion as for the LST-NGs. As shown in Figures 5 and 6, AFI also provided good-quality visualization of LST-G lesions for the less-experienced endoscopists, despite the lack of a significant difference in visualization quality between WLI and AFI for the experienced endoscopists. This result indicates that an advantage of AFI might be that it simplifies observations for less-experienced endoscopists. We also compared the backgrounds of the LST-NG lesions between those with good versus poor visualization quality by using AFI. There were no significant differences between lesions that had good versus poor visualization quality with respect to macroscopic

Table 2: Backgrounds of the LST-NG lesion evaluated by AFI in group A.

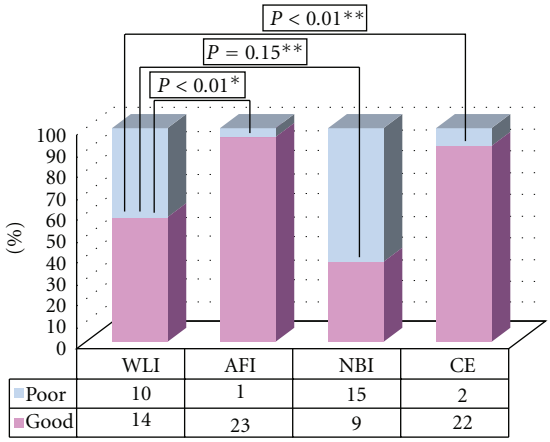
	Quality of visualization		
	Good	Poor	*P*
Macroscopic type			
Flat elevated	32	9	0.30*
Flat or flat depressed	4	2	
Lesion size (mm)			
Median	25	35	<0.05**
Range	20–50	20–60	
Location			
Rectum	6	1	0.34*
Cecum or colon	30	10	
Pathological finding			
Adenoma	4	2	0.30*
Adenocarcinoma	32	9	

* Fisher's exact test.
** Mann-Whitney test.

Table 3: Characterization of LST-NG lesions by AFI in group B.

	Quality of visualization		
	Good	Poor	P
Macroscopic type			
Flat elevated	16	25	0.07*
Flat or flat depressed	0	6	
Lesion size (mm)			
Median	25	30	<0.05**
Range	20–45	20–60	
Location			
Rectum	2	5	0.32*
Cecum or colon	14	26	
Pathological finding			
Adenoma	4	2	0.08*
Adenocarcinoma	12	29	

* Fisher's exact test.
** Mann-Whitney test.



*Fisher's exact test
**Chi-square test

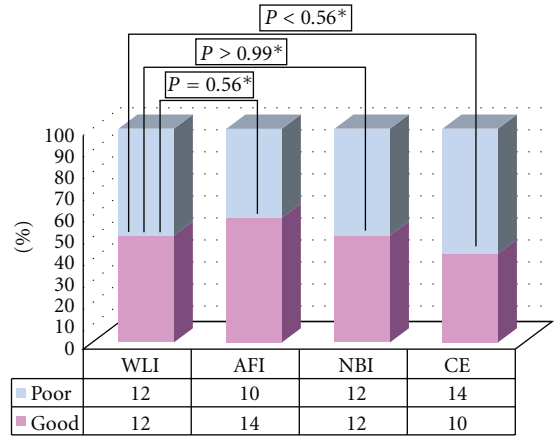
Figure 5: Visualization of LST-G in group A.

type, location, or pathological findings. However, the well-visualized lesions were larger than the poorly visualized lesions in groups A and B. To obtain a whole image of a large lesion, it is necessary to maintain sufficient distance between the tip of the scope and the lesion, which may affect the visibility of the lesion.

This study had several limitations. Only still images were evaluated, and it is uncertain if these findings can be applied to real-time video endoscopy. A relatively small sample precludes any multivariate analysis. Larger studies are needed to define the factors influencing the quality of visualization.

6. Conclusion

AFI provides good-quality visualization of LST-NG lesions on still images. However, to confirm the detectability of LST-NG lesions by using AFI, multicenter trials should be performed.



*Chi-square test

Figure 6: Visualization of LST-G in group B.

Conflict of Interests

All authors have no conflict of interests or financial ties to disclose.

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Clinical Study

Cost-Effectiveness of Total Colonoscopy in Screening of Colorectal Cancer in Japan

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Introduction. In Japan, the cost-effectiveness of total colonoscopy (TCS) for primary screening of colorectal cancer (CRC) is unclear. We compared the cost of identifying a patient with CRC using two primary screening strategies: TCS (strategy 1) and the immunochemical fecal test (FIT) (strategy 2). *Materials and Methods*. We retrospectively analyzed the TCS screening database at our institution from February 2004 to August 2010 (strategy 1, $n = 15,348$) and the Japanese nationwide survey of CRC screening in 2008 (strategy 2, $n = 5,267,443$). *Results*. 112 and 6,838 CRC cases were detected in strategies 1 and 2, costing 2,124,000 JPY and 1,629,000 JPY, respectively. The rate of earlier-stage CRC was higher in strategy 1. *Conclusions*. The cost was higher using TCS as a primary screening procedure. However, the difference was not excessive, and considering the increased rate of detecting earlier CRC, the use of TCS as a primary screening tool may be cost-effective.

1. Introduction

In Japan, the incidence and mortality rate of colorectal cancer (CRC) has increased significantly, with an incidence of approximately 100,000 cases and over 40,000 deaths per year [1]. CRC is now the second most commonly diagnosed cancer and the third leading cause of cancer-related mortality in Japan. In order to decrease the incidence and mortality of CRC, a screening system has been established. There are two types of CRC screening in Japan; one is population-based screening recommended for the entire population aging 40 and over, and the other is opportunistic screening. In population-based screening, the immunochemical fecal test (FIT) is used as a primary screening tool and total colonoscopy (TCS) is only performed for those with a positive FIT. TCS is not used as a primary screening procedure in population-based screening. On the other hand, in opportunistic screening, TCS is widely used as a primary screening procedure.

In this situation, the relative cost-effectiveness of different CRC screening strategies needs to be clarified. Such analyses have been performed in the United States and other countries [2–8], but in Japan, there have been limited analyses of the cost-effectiveness of CRC screening [9, 10], with the studies available demonstrating the population-based screening strategy to be cost-effective. In contrast, the cost-effectiveness of TCS as a primary screening strategy in opportunistic screening is still unclear.

In this study, our primary objective was to compare the cost of identifying a patient with CRC in Japan using two strategies: TCS as a first screen (strategy 1) versus FIT as a first screen (strategy 2).

2. Materials and Methods

We retrospectively analyzed the cost of identifying a patient with CRC using strategies 1 and 2 as follows.

2.1. Strategy 1: TCS as a Primary Screening. We retrospectively reviewed the database of the Cancer Screening Division,

Research Center for Cancer Prevention and Screening, National Cancer Center, which followed all subjects given a TCS as a primary screening from February 2004 to August 2010. A total of 15,348 cases had a colonoscopy performed as a primary screening. This data was used to calculate the cost associated with identifying a patient with CRC using the cost of TCS as 15,500 JPY, based on Japanese national reimbursement tables.

2.2. Strategy 2: FIT as a Primary Screening. We retrospectively analyzed the Japanese nationwide survey of CRC screening in 2008 [11]. A total of 5,267,443 cases were included. This data was used to calculate the cost associated with identifying a patient with CRC using the cost of FIT as 1,600 JPY and TCS as 15,500 JPY, respectively.

3. Results

Clinical characteristics of examinees in strategies 1 and 2 are listed in Table 1. Both groups predominantly comprised examinees in their 50s and 60s, and there was a higher male-to-female ratio in strategy 2 than in strategy 1. However, there was no statistical significance between two groups.

The number of CRC cases identified and the cost to find one case of CRC in both groups are listed in Table 2. In strategy 1, there were 112 cases of CRC among 15,348 TCS examinees (0.73%), with a calculated cost of finding one CRC case of 2,124,000 JPY. In group 2, 5,267,443 underwent FIT, with 319,846 cases testing positive, (6.1%). All examinees with a positive FIT were recommended for a further TCS. However, only 174,914 examinees (54.7%) underwent TCS, and 6,838 cases of CRC were found. The calculated cost to find one patient with CRC was 1,629,000 JPY in this group. If all of the 319,846 cases with a positive FIT had undergone TCS, the number of CRC cases would have increased, reducing the cost of identifying CRC. Assuming that the rate of CRC cases among the TCS examinees was the same as that in the strategy 2 group (3.9%; 6,838/174,914), it was calculated that there would be 12,504 CRC patients, each costing 1,090,000 JPY to be identified.

The staging of CRC at diagnosis (Japanese Classification of Colorectal Carcinoma) and initial treatment for CRC are summarized in Table 2. The rate of stage 0 and endoscopic resection were higher in strategy 1 than in strategy 2.

Table 1: Clinical characteristics of examinees in strategies 1 and 2.

	Strategy 1 ($n = 15,348$)	Strategy 2 ($n = 5,267,443$)
Screening strategy	TCS as a primary screening	FIT as a primary screening
Sex		
Male	5,892 (38.4%)	2,174,604 (41.3%)
Female	9,456 (61.6%)	2,006,926 (38.1%)
Unknown	0	1,085,913 (20.6%)
Age group (yr)		
<40	15 (0.1%)	370,750 (7.0%)
40–49	1,918 (12.5%)	870,134 (16.5%)
50–59	4,864 (31.7%)	1,050,813 (19.9%)
60–69	6,521 (42.5%)	1,044,313 (19.8%)
≧70	2,030 (13.2%)	845,520 (16.1%)
Unknown	0	1,085,913 (20.6%)
Mean (range)	60.1 (40–89)	Unknown

4. Discussion

Several previous studies have shown that CRC screening including FIT and TCS is cost-effective. However, in Japan, only a few cost-effective analyses have been reported, with the cost-effectiveness of TCS as primary screening still unclear.

In this analysis, we compared the cost of identifying a patient with CRC using two screening strategies, using TCS as a primary screening, or using FIT as a primary screening with TCS then performed in cases with a positive FIT test. The results demonstrated that it cost more to identify CRC when TCS was used as a primary screening strategy compared to the FIT screening strategy (2,124,000 JPY versus 1,629,000 JPY). It is assumed that this difference would have become even larger if all FIT-positive subjects had then chosen to have a TCS (2,124,000 JPY versus 1,090,000 JPY). However, the higher cost associated with the TCS only strategy does not necessarily deny the cost-effectiveness of this approach for primary screening. This is because TCS, used as a primary screening strategy, was able to identify CRC at an earlier stage as demonstrated in Table 2, possibly resulting in a decreased cost of CRC treatment and followup. The clinical course of the cases of CRC detected in strategy 1 at our institution is shown in Figure 1. Among the 112 CRC cases identified, 109 cases followed a clear clinical course, with approximately 80% cured with a single endoscopic treatment. Only one case has had recurrent disease following treatment. Such a clinical course indicates that earlier detection of CRC can lead to cure with less invasive treatment, resulting in a shorter period of followup and decreased cost of CRC care. From this perspective, it is possible to postulate that the difference in the cost of identifying CRC in the two strategies is not as great and that TCS may be a cost-effective primary screening strategy. Additionally, we probably underestimated the cost-effectiveness of TCS because we did not include the possibility to reduce CRC incidence with TCS in this study. Previous studies have demonstrated the effect of colonic polypectomy in reducing CRC incidence [12, 13]. Not only when using TCS as a primary screening strategy but also when using FIT as a primary screening, reduction in CRC incidence is expected [14]. However, taking into account the higher detection rate for colorectal polyps with TCS and the low rate of undergoing TCS among examinees with a positive FIT, reduction in CRC incidence is expected more when using TCS as a primary screening. If we consider this effect of TCS, TCS may be a more acceptable choice as a primary screening. Furthermore, considering that using TCS as a primary screening can lead to better quality of life (QOL) after CRC diagnosis due to the earlier detection of disease, it is worth performing TCS as a primary screening of CRC.

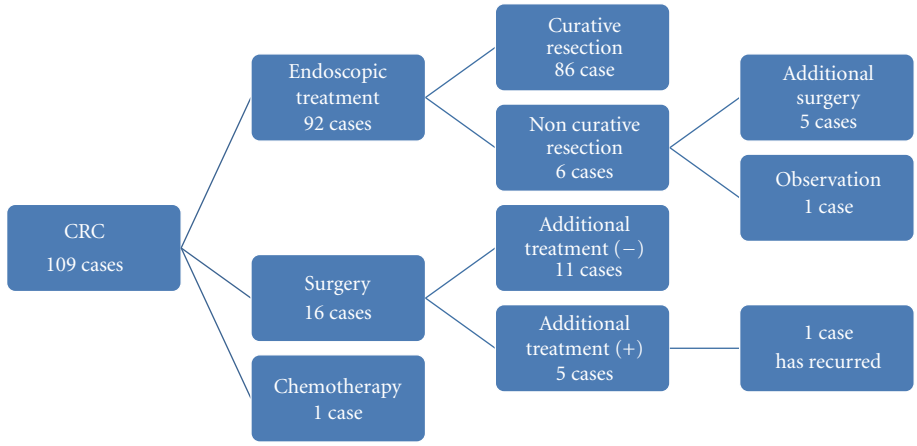

Figure 1: The clinical course of CRC cases detected in strategy 1.

Table 2: Number of CRC cases, the cost to find one CRC case, staging of CRC at diagnosis, and initial treatment for CRC in both strategies.

	Strategy 1 ($n = 15,348$)	Strategy 2 ($n = 5,267,443$)
Number of cases of CRC	112 (0.73%)	6,838 (0.13%)
Cost to find a case of CRC	2,124,000 JPY	1,629,000 JPY
Staging of CRC at diagnosis		
0	81 (72.3%)	1,713 (25.1%)
I	16 (14.3%)	1,043 (15.3%)
II	7 (6.3%)	552 (8.1%)
III a	3 (2.7%)	418 (6.1%)
III b	1 (0.9%)	187 (2.7%)
IV	1 (0.9%)	116 (1.7%)
Unknown	3 (2.7%)	2,809 (41.1%)
Initial treatment for CRC		
Endoscopic treatment	93 (83.0%)	2,267 (33.2%)
Surgery	16 (14.3%)	2,466 (36.1%)
No treatment	0	19 (0.3%)
Others	0	67 (1.0%)
Unknown	3 (2.7%)	2,019 (29.5%)

5. Conclusions

The cost associated with identifying one case of CRC is higher when using TCS as a primary screening strategy compared to using the FIT as a primary screening. However, taking into account the earlier detection of CRC using TCS, it is possible to postulate that the final cost difference may be reduced and that TCS may provide a cost-effective primary screening strategy. Additionally, considering the effect of TCS on CRC incidence and a better QOL after earlier detection of CRC with TCS, TCS is worth using as a primary screening of CRC.

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Research Article

What Would Make Getting Colorectal Cancer Screening Easier? Perspectives from Screeners and Nonscreeners

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Background. Despite the availability of multiple effective tests for colorectal cancer (CRC), screening rates are low. Greater understanding of barriers between screeners and nonscreeners may improve public health initiatives to increase CRC screening (CRCS). *Methods*. We conducted a content analysis of 625 responses to the question: "*Was there anything that would have made getting tested easier?*" Respondents were patients at a multispecialty practice who participated in a behavioral intervention trial to increase CRCS. Using clinic records, we classified patients as early-screeners (<6 months), late-screeners(6–12 months), and nonscreeners (>12 months). *Results*. Both screeners and nonscreeners reported the same categories of barriers. However, early-screeners predominantly cited dislike of test attributes such as bowel preparation, whereas nonscreeners cited concerns regarding finances and work and family responsibilities. *Conclusion*. Multilevel strategies that address scheduling barriers and external screening barriers may improve CRCS. Future studies may test hypotheses about mediators explaining how screeners overcome barriers.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in men and women in the USA [1]. Regular CRC screening (CRCS) is recommended beginning at age 50 for average-risk adults [1, 2]. Despite the availability of multiple tests for the early detection and prevention of CRC, screening rates are less than optimal [3, 4].

Considerable research including data from national surveys [5–10] and local studies [11, 12] have described reasons for not undergoing CRCS, but all were based on interviews with nonscreeners. National survey data from 2000 to 2005 consistently found that the two main reasons nonscreeners gave for not having CRCS were lack of awareness of the need for the test and lack of provider recommendation or order [5–10]. Other barriers identified in local studies of nonscreeners include absence of symptoms, being too busy, other health concerns, and logistical problems [11, 12]. Lack of awareness was not a primary reason given for not being screened, perhaps because most of the samples were patients within healthcare settings.

Very few studies have compared reasons given by screeners and nonscreeners in the same study sample [13–15], and findings were somewhat inconsistent. Greater understanding of the similarities and differences in the experience and concerns of screeners and nonscreeners may have important implications for interventions, patient-physician communication, and healthcare system practices and policies designed to increase screening. The purpose of this paper is to extend past research by investigating barriers to screening among patients from a single healthcare system who participated in a behavioral intervention trial to increase CRCS and who subsequently either did or did not complete screening.

2. Methods

2.1. Setting. The trial was conducted at Kelsey-Seybold Clinic, a large, multispecialty medical group practice in Houston, Texas, by the Kelsey Research Foundation and the University of Texas School of Public Health (UTSPH) (5R01CA097263; PI: Sally W. Vernon). The institutional review board at the UTSPH approved the trial.

2.2. Patients and Procedures. A data programmer at the foundation searched the clinic's administrative database to identify patients eligible for the trial with the following characteristics: received primary care at the clinic within the last year, were between 50 and 70 years of age, never had CRC or polyps, had never been screened or were due for CRCS according to American Cancer Society guidelines in effect at the time of the study [16], and had not had a physical exam within the past year. Other eligibility criteria were that patients had no prior diagnosis of Crohn's disease or ulcerative colitis; were English-speaking; had a wellness exam scheduled or were willing to schedule one; were willing to complete a baseline survey; agreed to come to the clinic 45 min before their exam to complete a study visit.

University research staff administered the baseline telephone survey and randomized patients to one of three study groups. All patients met with research staff approximately one hour prior to a physician visit for a wellness exam to review intervention materials, if applicable. Data was collected in 2004–2007. Patients were surveyed by telephone at baseline and 6 months. Additional details about the trial are reported elsewhere [17].

2.3. Measures. All participants were asked the following open-ended question on the 6-month survey: "Was there anything that would have made getting tested easier?" Research assistants recorded patients' responses using a web-based survey instrument. All responses were brief, consisting of a few words, a phrase, or a short sentence. Patients were not asked to explain or elaborate on their responses.

Screening status was ascertained from clinic records at 6 and 12 months after-intervention [17]. CRCS status was defined as completing one of the following tests post intervention: fecal occult blood test, sigmoidoscopy, colonoscopy, or double-contrast barium enema. Patients were classified as early-screeners (screened by 6 months), late-screeners (screened >6 months but ≤12 months), and nonscreeners (not screened by 12 months). Thus, early-screeners responded to the question after being screened, whereas late-screeners and nonscreeners had not been screened when they answered the question.

2.4. Data Analysis. Using ATLAS.ti, one of the authors (GM) conducted a content analysis beginning with an open-coding, iterative review of patient responses to identify an initial code list that classified, summarized and separated patient responses into similar concepts or units [18]. Following a constant comparison method, two of the authors (GM and AM) refined the code list and organized the codes into mutually exclusive categories and subcategories. We then compared the rank order of codes for each category and subcategory by screening status at followup to examine potential differences and similarities in the pattern and frequency of responses for the 3 groups. We chose not to examine codes by intervention group because the trial results showed no differences in screening rates by group [17], and a qualitative study involving a subset of trial participants found no meaningful differences in physician-patient discussions about CRCS by group [19].

3. Results

Baseline surveys were completed by 1224 patients, and 1026 of them completed the followup survey at 6 months post intervention. Of the 1026 respondents, we separated responses concerning barriers ($n = 625$), those simply saying "no," "none," or "nothing" ($n = 320$), and those respondents with no comments at all ($n = 81$). The three response groups were similar in gender, age, marital status, and employment status (Table 1). African-Americans were more likely than Whites or Hispanics to report no barriers. Those who responded "none" or "nothing" had less education and lower incomes compared with the other two groups. Early-screeners were more likely than late- or nonscreeners to report that nothing would have made screening easier. In contrast, nonscreeners were more likely than early- or late-screeners to report barriers.

For our main content analysis, we focused on the 625 respondents who reported barriers to CRCS. Our analysis sample was similar to our overall study sample [17] and was predominantly female, 50 to 59 years old, married, employed, had less than a college degree, and had an annual income of $30,000 or more.

We identified two mutually exclusive categories of responses to the question about what would have made getting tested easier: scheduling barriers and screening barriers. Scheduling barriers were sub-categorized into patient-related and system-related barriers. Patients' reasons for not scheduling CRCS were classified as patient-related, whereas responses related to patients' interaction with the clinic were classified as system-related scheduling barriers. Screening barriers were sub-categorized into external and internal barriers. Circumstances occurring or existing extraneous to patients yet exerting a strong influence on their CRCS decisions or actions were classified as external barriers. Responses that referred to patients' commitment to CRCS or their emotional and psychological reactions to CRCS were classified as internal barriers. Overall, early-screeners were least likely and late-screeners were most likely to report scheduling barriers (Table 2). In contrast, early-screeners were most likely and late-screeners were least likely to report screening barriers. Nonscreeners were equally likely to report both types of barriers.

3.1. Scheduling Barriers

3.1.1. Patient-Related Scheduling Barriers. Nonscreeners reported more "work and family responsibilities" and "being

Table 1: Socio-demographic characteristics of survey respondents ($N = 1026$) reporting barriers ($N = 625$), "no" or "nothing" ($N = 320$), or no comment ($N = 81$) on the 6-month followup survey.

	Reported barriers ($n = 625$)		No, nothing ($n = 320$)		No comment ($n = 81$)	
	n	%	*n*	%	*n*	%
Gender						
Females	367	58.7	184	57.5	45	55.6
Males	258	41.3	136	42.5	36	44.4
Race/ethnicity						
African-American	273	43.7	164	51.3	35	43.2
Hispanic	74	11.8	22	6.9	7	8.6
White	242	38.7	119	37.2	33	40.7
Other, unreported	36	5.8	15	4.7	6	7.4
Age group						
50–59	497	79.8	261	81.6	63	77.8
60+	128	20.5	59	18.4	18	22.2
Married						
Yes	382	61.1	200	62.5	54	66.7
No	239	38.2	119	37.2	27	33.3
Unreported	4	0.6	1	0.3	0	—
Employed						
Yes	508	81.3	253	79.1	64	79.0
No	114	18.2	64	20.0	16	19.8
Unreported	3	0.5	3	0.9	1	1.2
Education						
Less than college	346	55.4	187	58.4	52	64.2
College degree or higher	276	44.2	130	40.6	29	35.8
Unreported	3	0.5	3	0.9	0	—
Income						
< \$30 K	87	13.9	50	15.6	22	27.2
\$30 K–< \$70 K	284	45.4	137	42.8	27	33.3
\$70 K or higher	221	35.4	119	37.2	32	39.5
Unreported	33	5.3	14	4.4	0	—
Screening status						
Early-screener (<6 mo)	110	17.6	180	56.3	34	42.0
Late-screener (>6 mo but ≤12 mo)	39	6.2	12	3.8	0	—
Nonscreener by 12 mo	476	76.2	128	40.0	47	58.0

too busy" while more early- and late-screeners reported having a pending appointment (Table 2). The most common family responsibility involved providing care for ill spouses, children, and aging parents, some of whom suffered from illnesses such as cancer or Alzheimer's disease. Quotes illustrating patient-related scheduling barriers are included in Table 3.

3.1.2. System-Related Scheduling Barriers. Having difficulty scheduling an appointment was the most frequently mentioned system-related scheduling barrier among early- and late-screeners (Table 2). Waiting or expecting to be called by the clinic was the most frequently reported barrier mentioned by nonscreeners. Specific responses included reports about having trouble identifying a clinic appointment that fit their schedule (8 of 17 early- and late-screeners and 11 of 34 nonscreeners) and concerns about the wait time for getting an appointment (4 of 17 early- and late-screeners and 5 of 34 nonscreeners). One of 7 late-screeners and 5 of 34 nonscreeners reported that the clinic canceled their appointment, but they did not mention whether they or the clinic attempted to reschedule. The remaining 17 participants (4 of 17 early- and late-screeners and 13 of 34 nonscreeners) wanted the clinic to be more active regarding scheduling of appointments. Of 43 participants waiting or expecting to be called by the clinic, 1 of 3 screeners and 6 of 40 nonscreeners wanted the clinic to schedule the visit with the Gastroenterology Department instead of having to

Table 2: Types of scheduling and screening barriers reported by early-, late-, and nonscreeners ($n = 625$).

	Early-screener ≤6 months ($n = 110$)		Late-screener >6 months but ≤12 months ($n = 39$)		Nonscreener by 12 months ($n = 476$)	
	n	%	*n*	%	*n*	%
Scheduling barriers	27	24.5	30	76.9	233	48.9
	Rank	(*n*)	Rank	(*n*)	Rank	(*n*)
Patient related						
Being too busy	2–3	(3)	4	(3)	2	(50)
Work and family responsibilities	2–3	(3)	3	(5)	1	(61)
Missed appointment	4	(2)	2	(6)	3	(24)
Pending appointment	1	(7)	1	(7)	4	(17)
System related						
Patient had difficulty scheduling appointment with clinic	1	(10)	1	(7)	2	(34)
Patient expected to be called by clinic	2	(2)	2-3	(1)	1	(40)
Patient preferred direct access to colonoscopy	—	(0)	2-3	(1)	3	(7)
	n	%	*n*	%	*n*	%
Screening barriers	83	75.5	9	23.1	243	51.1
	Rank	(*n*)	Rank	(*n*)	Rank	(*n*)
External						
Financial/insurance concerns	2	(12)	2	(2)	1	(68)
Medical conditions	3	(4)	1	(3)	2	(56)
Patient disliked screening test attributes	1	(44)	3-4	(1)	3	(20)
Perceived lack of physician direction	—	(0)	—	(0)	4	(15)
Transportation needs	4	(3)	3-4	(1)	5	(14)
Internal						
Salience for screening	3	(4)	1	(2)	1	(30)
Perceived low need to screen	4	(1)	—	(0)	2	(23)
Wanted more information	1	(9)	—	(0)	4	(2)
Emotional concerns including fear of pain or discomfort	2	(6)	—	(0)	3	(15)

Barriers are rank ordered within subcategories.

schedule it themselves. One late-screener and 7 nonscreeners wanted direct access to colonoscopy after completing a wellness exam rather than having to schedule a consultation with a gastroenterologist prior to scheduling an endoscopic procedure, the protocol in effect during the study. Sample quotes of system-related scheduling barriers are included in Table 3.

3.2. Screening Barriers

3.2.1. External Screening Barriers. For nonscreeners, the most frequently reported external barrier was financial or lack of insurance coverage for CRCS; this barrier was the second most frequently mentioned barrier among both early- and late-screeners (Table 2). Although all participants had health insurance at baseline, screeners and nonscreeners still considered CRCS to be too expensive and reported out-of-pocket costs (e.g., copays or deductibles) ranging from a few hundred to a few thousand dollars. Five of the 14 early and late-screeners had a colonoscopy and reported that the copay was unexpectedly high. Two screeners had previously postponed or rescheduled their appointments due to the copay amount. The remaining 7 screeners who thought the cost was too high completed a stool blood test, which is usually covered by insurance, so it may be that they thought the other tests were too expensive.

Medical conditions were the second most often reported external barrier among nonscreeners (Table 2). Of the 56 nonscreeners, 8 reported having heart problems, 10 reported having surgeries, and 15 reported chronic conditions such as diabetes, arthritis, multiple sclerosis, and cancer. Of the 23 remaining nonscreeners, all reported having acute health concerns that required their immediate attention or financial resources. In contrast, only 4 of the 63 early-screeners who reported external barriers cited medical conditions as a barrier. Although late-screeners ranked medical conditions first among all external screening barriers, only 7 late-screeners reported this barrier.

Dislike of screening test attributes was the most frequently reported external barrier among early-screeners; it was less

Table 3: Selected illustrative quotes.

Patient-related scheduling barriers
My own scheduling issues (early-screener).
If I had more flexible times available (late-screener).
I am a teacher. Once the school year has ended, I can set up a time (nonscreener).
My daughter has been ill for the last six months. I have to drive my daughter and I have care-giving duties for my mother (nonscreener).
I have tried to be tested several times but have had to reschedule. I am scheduled for my GI consultation February 13 with Dr. [name withheld] (nonscreener).
System-related scheduling barriers
I tried to schedule but a convenient time has not been found (nonscreener).
When I called to get a colonoscopy, they told me to get a consult. I did not see the use of the consult. It could be done right before the colonoscopy (nonscreener).
I'm waiting for them to call me back so that I can get a colonoscopy (nonscreener).
External screening barriers: financial/insurance barriers
I would have liked to have known how much it was going to cost. I would not have done it at that time (early-screener).
I had a problem coming up with the deductible, so I had to reschedule (late-screener).
Although I was scheduled, I could not afford the copay (nonscreener).
I changed insurance and the new insurance would not cover as much of it. It would have been very expensive (nonscreener).
External screening barriers: medical conditions
Because I had the flu and the doctor directed me to postpone having the colonoscopy (early-screener).
I had a physical problem-bad hemorrhoids (late-screener).
I had a heart condition that required hospitalization and caused me to postpone my plans for screening (nonscreener).
I have had several health problems. I cannot think of colon cancer screening (nonscreener).
External screening barriers: patients disliked screening test requirements
Drinking the water/prep was the problem (early-screener).
The laxative stuff is hard to get through (early-screener).
The drink that you have to drink was horrible. If that tasted better (early-screener).
If they had an easier testing process like swallowing a camera. I do not like the purging process (nonscreener).
If I did not have to do the FOBT at all—it was kind of a hassle since I had to do it over 3 days at home (nonscreener).
External screening barriers: perceived lack of physician direction
At the physical, the physician did not push me to do any screening (nonscreener).
My doctor's decision would have made it easier, but the doctor is still telling me to wait and see (nonscreener).
External screening barriers: transportation needs
I felt that I could have driven myself home after the test. That is what kept me from doing it sooner. I had to find someone to drive me there (early-screener).
I do not have anyone to drive me to the testing for a colonoscopy (nonscreener).
Internal screening barriers: low salience for screening
No. It's just me. I'm trying to plan around work and I'm just lazy (late-screener).
Just not on my radar right now (nonscreener).
I have a FOBT kit, but I have not done the test (nonscreener).
Internal screening barriers: low perceived need for CRCS
If I thought I had symptoms and was ill then I would have been tested (early-screener).
I do not feel a need for it. My stools are ok and I feel ok (nonscreener).
At the doctor's office, they did a rectal exam. They did not recommend anything further. I thought that was all that was needed (nonscreener).
Internal screening barriers: information needs
Maybe seeing a video clip from an actual screening procedure to be better prepared for what is going to happen during the test (early-screener).
I would have liked more information about the procedure (nonscreener).
Internal screening barriers: emotional concerns
I did not feel anything during the procedure and I think it would have been easier to get tested if I had known that I really would not have any pain (early-screener).
It would help me complete testing if I could take away some of the fear of the procedure (nonscreener).

GI: gastroenterology; CRCS: colorectal cancer screening; FOBT: fecal occult blood test.

often mentioned by late- and nonscreeners (Table 2). Overall, 47 of the 65 participants who disliked the screening test attributes specifically disliked the bowel preparation including the large volume of liquid, taste, and laxative effect. Of these 47 responses, 38 were from screeners, which may reflect experience with the test. The remaining 18 participants (7 early-screeners and 11 nonscreeners) reported disliking other CRCS test attributes, namely the invasiveness of endoscopies, the inconvenience of a stool blood test, and in a few cases, sedation. Both early-screeners and nonscreeners reported wanting alternative tests such as a virtual colonoscopy or ultrasound. The least frequently mentioned external screening barriers by all 3 groups were lack of physician direction and transportation needs (Table 2). Only nonscreeners mentioned lack of physician direction as a barrier. Sample quotes illustrating all external personal barriers are included in Table 3.

3.2.2. Internal Screening Barriers. For nonscreeners, the two most frequently reported internal screening barriers were low salience and low perceived need to be screened (Table 2). Participants responded that they had forgotten, remained undecided or had "just not gotten around to it." In contrast, 3 of 4 early-screeners indicated high salience for CRCS by describing it as a task that simply had to be completed or as one early-screener said, "I did not even stop to think about it—I just got it done." For early-screeners, the two most frequently reported responses were wanting more information about screening and having emotional concerns such as fear of pain, anxiety about screening, unpleasantness of the test, inconvenience, humiliation, and reluctance to get tested (Table 2). These concerns were less frequently reported by nonscreeners; however, all 3 people who anticipated pain from the test procedure were nonscreeners. All 6 screeners who listed emotional concerns noted that their fears were unfounded due to sedation before the colonoscopy. Quotes illustrating internal barriers are included in Table 3.

4. Discussion

Although there was overlap in the rank order of responses from screeners and nonscreeners, we observed some noteworthy differences. For early-screeners, who answered our question after being screened, dislike of test attributes such as bowel preparation, an external screening barrier, was the predominant response. Of 110 early-screeners, 44 said a different preparation or an alternative test that did not involve bowel preparation would have made screening easier compared with 20 of 476 nonscreeners. It is unknown whether bowel preparation was perceived to be a barrier prior to screening by early-screeners in this study, but our findings are similar to other reports in the literature. Although study methods differed, Jones et al. [13] found that bowel preparation ranked first as a barrier for patients who were up-to-date with colonoscopy and for those overdue for sigmoidoscopy or colonoscopy, but not for those never screened. In contrast, Harewood et al. [15] found that not wanting to do the bowel preparation for colonoscopy was the highest ranked reason among both never screeners and among those who had been screened previously. In a study of complications following colonoscopy, 77% of patients reported the bowel preparation as the worst part [20]. In previous studies of nonscreeners only, test preparation was rarely listed among the top five barriers, [11, 12] even in studies that focused on colonoscopy [12]. Although these inconsistent findings may be due to differences in study methods, they leave unresolved the question whether apprehension of or experience with bowel preparation affects both first-time and repeat testing. Providing patients with more detailed information about test attributes and alternatives could help them cope and could increase self-efficacy. Consistent with this idea, screeners reported wanting more information about the screening process.

For nonscreeners, the most frequently cited response was financial and insurance concerns. Very few early-screeners raised this issue (12 of 110 early-screeners). These findings are generally consistent with Jones et al. [13] who found that cost ranked second among screeners and third among those who were overdue. However, Denberg et al. [12] noted that most of the patients who voiced finances as a barrier actually did not know whether colonoscopy was covered by their health insurance plan and the copay amount. Further research is needed to assess patient's willingness to pay for preventive screening.

Nonscreeners frequently mentioned that being too busy and work and family responsibilities were reasons they deferred scheduling CRCS. In contrast, these reasons were infrequently mentioned by early- and late-screeners. Although CRCS does require a time commitment, Denberg et al. [12] speculated that responses from patients about being "too busy" may have obscured motivational barriers. Nonscreeners may benefit from screeners' accounts about how they successfully scheduled and prepared for a test, es-pecially those with more negative feelings about the test procedure or preparation [15].

Compared with screeners, nonscreeners cited medical conditions as an important barrier with many reporting chronic health conditions. Although patients with medical conditions may have more frequent contact with the healthcare system and subsequently more opportunities to be offered screening, prevention may not get addressed. Future research should examine how patients, along with their physicians, prioritize and address multiple health concerns, including preventive health behaviors.

The followup survey may have served as a reminder to nonscreeners to get CRCS [21]. In our study, 39 of 515 nonscreeners at the 6-month survey were later classified as late-screeners because they were adherent by 12-month followup. Late-screeners in our sample may reflect more motivated screeners who were temporarily delayed by barriers. Specifically, patient-related and system-related scheduling barriers were the barriers most frequently mentioned by this group. Other studies also have found scheduling challenges at the system-level [12]. Scheduling issues may reflect patients' lack of flexibility in scheduling appointments, lack of understanding of the screening process, or inability to navigate the healthcare system. Attempts to make CRCS

easier for patients such as offering the stool blood test, enabling direct-access colonoscopy, using patient navigators to assist patients through the process, and combining CRCS with other preventive care services (e.g., flu shots [22]) might increase screening rates. Additionally, we found that a small number of patients expected to receive a call from the endoscopy clinic suggesting a desire for more clinic outreach efforts to schedule patients.

In contrast to national data, lack of awareness was not frequently mentioned as a reason not to get screened by any of the 3 groups. Other data from our study showed that physicians consistently brought up CRCS during the exam; however, in general, they did not engage in much discussion or facilitate appointment scheduling [19]. Nevertheless, most patients probably received a recommendation to be screened and were aware of the need to do it. This circumstance may explain our finding that lack of physician recommendation was not cited as a barrier to getting tested, nor did anyone specifically indicate that they were confused by the test options in any of the 3 groups.

CRCS rates are lower among males, whites, and people with lower education, income, and no insurance [23]. Barriers and test preferences may be different among these groups and could be compared in future studies. In our sample, everyone had insurance and baseline preferences by test type and screening rates at 12-month followup did not differ by gender, race/ethnicity, and education [17, 24].

Although we observed interesting differences in the most frequently reported barriers among screeners and nonscreeners, all three groups reported similar categories of barriers. Our results suggest that screeners were better able to overcome some barriers that hindered nonscreeners. Additionally, more early-screeners reported "no" barriers, whereas more nonscreeners reported barriers. Future studies should test hypotheses about mediators or moderators that explain how screeners overcome CRCS barriers. Several limitations should be considered in interpreting our findings. Our question referred to "any" CRCS test. The rank order of responses may have been differed had we asked test-specific questions like Jones et al. [13]. However, our findings suggest that most respondents focused on colonoscopy when discussing barriers to CRCS (especially the scheduling barriers category which is not relevant for stool blood tests). Respondents' focus on colonoscopy is consistent with physicians' consistent recommendations for COL [19] and the fact that most screeners got colonoscopy (57%) [17]. Because most previous studies have only queried nonscreeners, we think it is a strength that our study examined barriers among both screeners and nonscreeners. Further, our open-ended question may have elicited more salient barriers to CRCS irrespective of test type compared with an approach where patients rate a list of investigator-selected barriers. Although the wording of our question allowed us to query both screeners and nonscreeners, the word "easy" may have directed participants' attention to difficulties (e.g., bowel preparation) or barriers (e.g., financial/insurance), rather than to motivational factors or perceived importance of CRCS. Further, early-screeners' responses may be less comparable to nonscreeners because our question did not require them to focus on their barriers prior to screening only. Future studies could examine differences in perceived barriers before and after CRCS to better understand how the procedure influences perceptions. Additionally, we did not probe responses to the open-ended question which may have led to an understanding of how and why screeners overcame their barriers. We also may not have identified all barriers relevant to patients in the lowest category of education and income who were less able or willing to answer the open-ended question. Finally, although many of our findings are consistent with those of other local studies, the generalizability of these findings may be limited because the sample was drawn from a single healthcare system. In terms of our analysis, there was the possibility for misclassification of responses to the open-ended question. However, our team-based approach to coding responses and our process of iterative data analysis, we believe, minimized misclassification.

5. Conclusions

Screeners and nonscreeners expressed a range of challenges that may require different solutions including multilevel strategies that address both patient- and system-related scheduling barriers and strategies that address external screening barriers such as cost, dislike of bowel preparation, and medical conditions. Changes at the system-level that may increase CRCS rates include improving scheduling procedures, increasing direct access to colonoscopy, and use of patient navigators. Overcoming external screening barriers like cost will require policy changes that cover copayments while addressing screening barriers such as dislike of bowel preparation may require educational and motivational approaches. Healthcare providers should consider patients' individual needs and barriers when recommending CRCS. In summary, to accomplish the goal of increasing CRCS, it may be necessary to use multiple strategies targeting patients, physicians, and healthcare systems simultaneously.

Conflict of Interests

The authors declare no conflict of interests.

Acknowledgments

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Review Article

Application of Autofluorescence Endoscopy for Colorectal Cancer Screening: Rationale and an Update

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As the result of basic researches, several intravital fluorophores have been determined so far in human colorectal tissue. Autofluorescence endoscopy (AFE) can detect slight alterations in their distribution and concentration during the colorectal carcinogenesis process and, thus facilitate noninvasive screening colonoscopies without the need for fluorescent substances or staining reagents to be administered. While detecting faint autofluorescence intensity by conventional fiberoptic endoscopy remains challenging, the latest AFE system with high-resolution videoendoscope capabilities enables such detection by using a false-color display algorithm. To this end, the diagnostic benefits of AFE have been reported in several multicenter randomized controlled studies of colorectal cancer (CRC) screening and differential diagnosis. CRC screening using the latest AFE technology could, therefore, lead to future reductions in CRC mortality.

1. Introduction

Early detection and removal of colorectal adenomatous polyps is essential in reducing the mortality rate of colorectal cancer (CRC). Although there are several modalities for CRC screening, colonoscopy is considered the most effective procedure, allowing direct visualization and on-site treatment of the encountered lesions. However, minute or flat-type polyps are hard to detect even by conventional colonoscopy [1]. Narrow-band imaging (NBI) has been widely applied for the diagnosis of colorectal neoplasm during colonoscopy [2–4]. However, recent prospective studies [5–7] failed to show the effectiveness of NBI in screening colonoscopies.

Autofluorescence endoscopy (AFE) is now attracting attention for its potential in improving diagnostic yields for CRC. This technology was shown to detect slight alterations in autofluorescence intensity in the colorectal wall during the carcinogenesis process [8, 9].

2. Principle of AFE

2.1. Fluorophores in Human Colorectal Tissue. When light is focused onto a molecule, part of the light energy is reflected or scattered, and the rest is absorbed. The energy status of the molecule shifts from a ground state to a high-vibration energy state—this is known as excitation. Excess energy is emitted as thermal energy or consumed as vibrational energy when the molecules revert to their ground state. However, naturally fluorescent molecules in tissue release such excess energy as autofluorescence, which can be detected and measured.

Fluorophores determined so far in human colorectal tissue include collagen, which forms the basement membrane and the submucosal layer, NADH and FAD, which exist mainly in gland cell mitochondria and lysosomal granules, and porphyrin in the mitochondria of red blood cells and gland cells.

Autofluorescence emission has been reported mainly with respect to collagen distributed throughout the submucosal colorectal layer [8], with lower autofluorescence intensity also detected in neoplastic tissues. This reduced intensity is attributed to the attenuated optical penetrability, both for the excitation light and the autofluorescence, caused by the increased mucosal thickness and glandular density of neoplasm [9].

2.2. Fluorescence Endoscopy. Several studies focusing on fluorescence endoscopy combined with topical application of fluorescent substances such as porphyrin [10], tetracycline [11], or fluorescein [11] from the mid-20th century failed to reveal a diagnostic value. Low tissue specificity and technology deficits resulted in a failure to detect faint fluorescence intensity. However, a recent prospective study by Mayinger et al. [12] on the detection rate of colonic neoplastic lesions by photodynamic diagnosis (PDD) using fluorescence endoscopy (13902 PIKS; KARL STORZ, Tuttlingen, Germany) with topical application of 5-aminolevulinic acid (5-ALA), a precursor of porphyrin, and hexaminolevulinate (HAL), a derivative of 5-ALA, found that both applied fluorophores have an affinity for neoplastic tissues. In their study, PDD detected 28% more neoplastic lesions than white light endoscopy (WLE). Although PDD carries the inherent risk of complications such as photosensitivity, the modality has shown favorable diagnostic yields for detecting dysplasia in patients with ulcerative colitis [13] and Barrett's esophagus [14].

2.3. Autofluorescence Endoscopy. AFE detects intravital fluorescent substances without administration of exogenous fluorescent agents. Firstly developed as an autofluorescence bronchoscope (light-induced fluorescence endoscopy: LIFE, Xillix Technologies, British Columbia, Canada) [15], the technology was consequently applied to gastrointestinal endoscopy (LIFE-GI) [16]. This system uses analog equipment based on a fiberoptic endoscope and displays the ratio of green and red autofluorescence intensities as false color. A study in 2001 by Haringsma et al. [17] revealed that AFE based on this technology successfully visualized flat lesions 10 mm or larger in size, which were difficult to detect by WLE. However, this system had practical use problems in a clinical setting, as it was equipped with a heavy camera attached to the endoscope eyepiece [18].

The autofluorescence imaging system from Olympus (AFI system) is the latest AFE system and is equipped with high-resolution videoendoscope capabilities (CF-FH260AZI, Figure 1). This system uses a switching function between the WLE and AFE mode and the NBI mode, a zoom function, and variable stiffness function. Figure 2 sets out mechanistic details of the AFI system, in which false color images are ultimately produced by allocating the amplified autofluorescence signal to the green (G) channel and the reflected signal of green light to the red (R) and blue (B) channels in the ratio of 1 to 0.5. The endoscopic image is displayed in false color; areas with low and high autofluorescence intensity are shown in purple and green tones, respectively. Figure 3(a) shows a WLE image of a 5-cm lateral spreading tumor (granular type) in cecum, which is displayed by AFE as purple, thus, providing a strong color contrast with the surrounding normal mucosa shown in green (Figure 3(b)).

Figure 1: High-resolution videoendoscope (CF-FH260AZI) used in the autofluorescence imaging system (Olympus Medical Systems Corp, Tokyo, Japan).

A comparative study [20] between the LIFE-GI and AFI systems for differentially diagnosing hyperplastic lesions from colorectal adenomas revealed that sensitivity and specificity were 87% and 71% for LIFE-GI and 89% and 81% for AFI, respectively.

3. AFE in CRC Screening

Based on the advantage of AFE that colorectal lesions are displayed in purple, which is like a "red flag" in the surrounding normal colorectal mucosa shown in green, several randomized clinical trials have focused on the diagnostic utility of AFE in screening by colonoscopy. In a randomized controlled study using the AFI system [21], a modified back-to-back colonoscopy using AFE and WLE was conducted for 167 patients in the right-sided colon by a single, experienced colonoscopist. The patients were randomized to undergo the first colonoscopy with either AFE or WLE (group A: AFE-WLE, group B: WLE-AFE). Among all detected polyps, the number of neoplastic lesions detected by AFE and WLE colonoscopy was 92 and 69, respectively. Among 66 neoplastic lesions detected in group A, 47 (71%) were detected at the first AFE. In contrast, among 95 neoplastic lesions in group B, only 50 (53%) were detected at the first WLE, and 45 (47%) lesions were detected by the subsequently performed AFE. This indicated that significantly more neoplastic lesions were missed by WLE compared with AFE ($P = 0.02$).

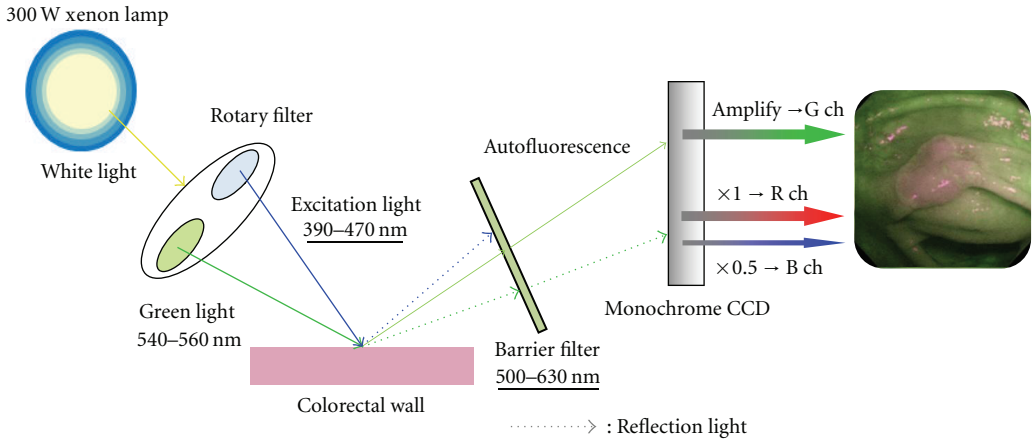
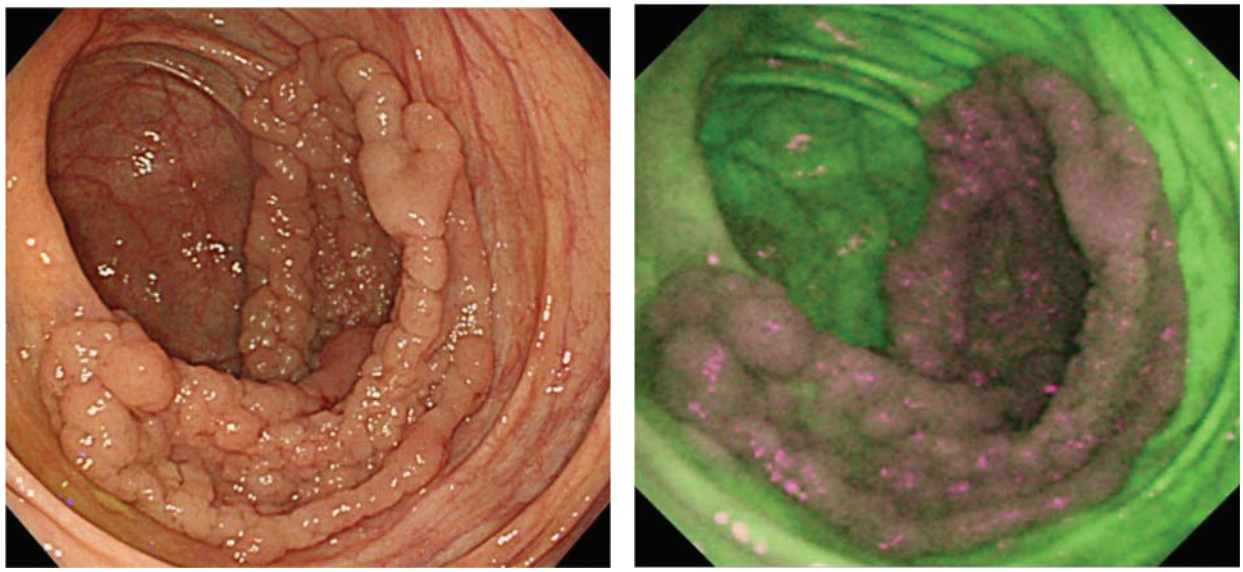


Figure 2: Schematic diagram of the AFI system [19]: white light emitted from a 300-W xenon lamp in the light source is separated with a rotary filter into an excitation light with a wavelength range of 390 to 470 nm and a green light of 540 to 560 nm wavelength. These fractionated lights radiate sequentially during the observation period. A barrier filter to remove reflected excitation light is set in front of a monochrome charge-coupled device. Light of 500 to 630 nm wavelength is selectively detected from both autofluorescence and reflected green light. A false color image is produced by allocating the detected and amplified autofluorescence signal to the green (G) channel and the reflected signal of green light to the red (R) and blue (B) channels in the ratio of 1 to 0.5.



(a) (b)

Figure 3: WLE image of 5-cm lateral spreading tumor (granular type) in cecum (a). With AFE, the lesion appears purple, which provides a strong color contrast with the surrounding normal mucosa shown in green (b).

A back-to-back comparative study by Ramsoekh et al. [22] analyzed the sensitivity of AFE and WLE for the detection of colorectal adenomas in high-risk patients from families with the Lynch syndrome or familial CRC. A total of 75 asymptomatic patients were examined with either WLE followed by AFE or AFE followed by WLE. Back-to-back colonoscopy was performed by two blinded endoscopists. WLE identified adenomas in 28/41 patients and AFE in 37/41 patients, representing a 32% difference in detection efficacy. In total, 95 adenomas were detected, 65 by WLE and 87 by AFE, indicating a significantly higher sensitivity of AFE compared with WLE (92% versus 68%; $P = 0.001$). In addition, the additionally detected adenomas with AFE were significantly smaller than the adenomas detected by WLE (mean 3.0 mm versus 4.9 mm; $P < 0.01$).

Although early detection and removal of colorectal adenomas is considered the most effective way of preventing colorectal cancer progression [19, 23], the impact of these reported higher detection rates of adenomas by AFE on CRC screening is still unclear due to the relatively small study populations tested thus far. Moreover, whether AFE is useful for detecting those depressed colorectal lesions with higher

malignant potential is still unclear. These points should be verified in future large-volume multicenter trials.

4. AFE in the Differential Diagnosis of Colorectal Neoplasm

The false color range in AFE is determined based on the calculation of balance between autofluorescence intensity and reflected green light intensity (Green/Red, G/R ratio), and this balance could be affected by thickness of the lesion, degree of vascularity, and glandular density. We numerically analyzed the color tone of colorectal lesions in AFE using special color analysis software [24]. A total of 103 colorectal lesions (22 nonneoplastic and 81 neoplastic lesions) were analyzed, and the mean G/R ratio was significantly higher in nonneoplastic lesions (1.17 (95% CI, 1.10–1.24), $n = 22$) than in neoplastic lesions (0.65 (95% CI, 0.63–0.68), $n = 81$) ($P < 0.001$). Under receiver operating characteristic analysis, with a cut-off value of 1.01 for G/R ratio, it was shown that AFE had a sensitivity and specificity of 98.8% and 86.4%, respectively. This result indicated that the color tone in AFE might directly visualize pathological features of colorectal lesions, and its analysis may facilitate the automated optical diagnosis of colorectal neoplastic lesions in the future.

5. Limitations of the AFI System

Despite more advantages with the latest AFE technology, the system still has some limitations that need to be overcome for its full potential to be realised. The outside diameters of the distal end and insertion tube are relatively thick (14.8 and 13.2 mm, resp.) compared to those used in conventional colonoscopy. This might limit maneuverability and, thus, hinder polyp detection, especially of those lesions harbored behind folds or flexures. Use of a transparent hood (TH) in AFE was shown to improve detection rates for colorectal neoplasms [25]. In this study, 561 patients were allocated among four groups: WLE alone, WLI without TH; WLI + TH, WLE with TH; AFE alone, AFE without TH; AFI + TH, AFE with TH. The neoplasm detection rate (95% confidence interval) in the AFI + TH group was significantly higher than that in the WLE alone group (1.96 [1.50–2.43] versus 1.19 [0.93–1.44]; $P = 0.023$).

The AFI system has two other limitations—delayed display and low image resolution. In our system, both video-frame rate and image resolution were reduced to create false-color images employing very faint autofluorescence intensity. In the future these factors should be overcome with system refinements so that CRC screening using this technology becomes more practical.

6. Conclusion

In this paper, we reviewed several papers that focused on the diagnostic value of AFE for CRC screening. We anticipate that AFE may contribute to future reductions in CRC mortality.

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Review Article

Factors Influencing Colorectal Cancer Screening Participation

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Colorectal cancer (CRC) is a major health problem worldwide. Although population-based CRC screening is strongly recommended in average-risk population, compliance rates are still far from the desirable rates. High levels of screening uptake are necessary for the success of any screening program. Therefore, the investigation of factors influencing participation is crucial prior to design and launches a population-based organized screening campaign. Several studies have identified screening behaviour factors related to potential participants, providers, or health care system. These influencing factors can also be classified in non-modifiable (i.e., demographic factors, education, health insurance, or income) and modifiable factors (i.e., knowledge about CRC and screening, patient and provider attitudes or structural barriers for screening). Modifiable determinants are of great interest as they are plausible targets for interventions. Interventions at different levels (patient, providers or health care system) have been tested across the studies with different results. This paper analyzes factors related to CRC screening behaviour and potential interventions designed to improve screening uptake.

1. Introduction

Colorectal cancer (CRC) is the third leading cancer worldwide in terms of incidence accounting for 1.2 million new cases in 2008 (9.7% of total cancers) and the most common malignancy in developed regions (727.000 cases). CRC mortality rates rank fourth after lung, stomach, and liver cancer accounting for 608.000 deaths in 2008 and 8% of all cancer deaths [1].

The efficacy of CRC screening in terms of reduction of incidence and mortality rates has been shown in randomized controlled trials [2–6]. In fact, medical organizations and practice clinical guidelines recommend screening in average-risk population [7–9]. In this way, the most extended CRC screening strategies are based either on annual or biennial faecal occult blood tests (FOBTs), with colonoscopy reserved for patients testing positive, or on endoscopic procedures performed as the primary screening tool performed once only every five years (sigmoidoscopy) or every ten years (colonoscopy). In addition, other screening procedures such as CT colonography and faecal DNA analysis have been recently recommended by some associations [8, 9] although available evidence has been considered insufficient by others [7].

Screening uptake, defined as a cross-sectional assessment of compliance is a critical determinant of success for any population-based screening program. High rates of participation has been consistently associated with screening efficacy in terms of mortality reduction as well as cost-effectiveness [10]. This assumption is particularly certain in the case of FOBT-based screening in which recommended intervals are shorter than for other screening strategies (every 1 or 2 years) [11, 12].

Recently, a report from the European Commission considered a minimum uptake of 45% in average-risk population as an acceptable goal and 65% as a desirable rate [13], whereas for the American Cancer Society the desirable goal is 75% of the average-risk population [14]. However, despite the available evidence and specific guidelines, CRC screening rates remain far from these aims, although a considerable variability exists around the world. In this way, population-based FOBTs and sigmoidoscopy programmes ranged from 7.2% to 90.1% and from 7% to 55%, respectively, in European countries. In the USA, according to the National

Health Interview the proportion of adults older than 50 years who had had a recent screening test ranged from 53% to 73% [14]. However, participation rates for CRC screening are markedly lower than those of other recommended adult preventive services [15]. Therefore, it is important to identify predictors of screening uptake and develop interventional strategies for promoting screening behaviours.

2. Predictors of Screening Uptake

Much attention has been given to investigate factors influencing CRC screening participation in average-risk population. A practical way to classify these factors is in non-modifiable factors (i.e., demographics, income, educational level, medical insurance, or family history) and modifiable factors, defined as those susceptible of intervention. Theories of health behaviour or theoretical models have been developed to understand why people do or do not practice different health behaviours, identifying modifiable factors which may be plausible targets of interventional strategies [16, 17]. These factors include knowledge about CRC and screening, perception of risk for developing a CRC, and benefits and barriers against screening or intention to be screened [18]. Therefore, theoretical models have a dual purpose, "explanatory" and "interventionist". Hereafter, we describe the factors influencing CRC screening.

2.1. Sociodemographic Factors. Mixed results have been reported regarding the influence of gender in screening participation. Although, overall, men look to participate more often than women in CRC screening, differences have been found depending on the country and screening strategy. In this way, a recent systematic review [19] showed a higher participation of women in FOBTs-based screening programmes carried out in Europe or Australia. Other studies suggest a higher use of endoscopy among men [20]. In USA, the Behavioral Risk Factor Surveillance System (BRFSS) surveys have consistently reported greater prevalence of CRC test, used among men compared with women [21]. However, generally in pooled analysis data, gender tended to be not significant [10].

Several studies have addressed the association between age and screening uptake [22–26]. In USA [24, 25], screening uptake was superior in elderly (≥65 years) people reporting a peak at 75 years and decreasing around 80–85 years. This finding could be explained, at least in part, because Medicare covers all recommended screening strategies in people older than 65 years, overcoming the economic barrier. However, the same observation was found in a randomized study performed in Italy [27], where men and women aged 65 years or older experienced a significant increase in screening uptake as compared to younger invitees.

Disparities in screening uptake have been consistently reported in ethnic minorities across the studies [14, 21, 28, 29]. The knowledge of barriers in these groups are of great interest to develop specific intervention strategies. Low income and low educational level have been associated with poor participation rates in minority ethnic groups [28, 29]. These factors could be more important in countries without a universal health coverage. In this regard, screening uptake has been consistently reported lower among minority groups as African Americans or Hispanics in USA [14, 21]. These data contrast with the higher reported incidence and mortality rates observed in African Americans compared with white population (20% and 45% higher incidence and mortality rate of CRC, resp.) [28, 29]. Other factors, such as language difficulties and the expression of culturally influenced health beliefs have been reported in different countries as barriers, independent of the health care system [30, 31]. In this way, information about test procedures and benefits of CRC screening provided by a native-speaking health educator has been suggested as a facilitator for increasing screening uptake in minority ethnic groups [32].

A low socioeconomic status (income, unemployment, educational level, and residence) has been associated with lower screening participation in many studies [14, 21, 33, 34]. This factor is more important in countries in which health services are not government funded. Data coming from the BRFSS surveys [21] consistently report a lower prevalence of CRC screening in those groups with lower hosehold incomes, persons with no health insurance, and unemployed. Lower education, assessed in different studies as less than high school education or having few years of education, has also been reported as a barrier for screening [15, 20, 29] regardless the type of screening strategy used [35]. In an European study carried out in 953 average-risk participants, the ever use of CRC screening being up-to-date screening was more than four times higher among participants with high education level [15]. Although an urban area of residence have been associated with higher rates of screening uptake in US studies [28, 36], contradictory results has been found in Europe [15, 37, 38]. For example, whereas a Swedish study found higher CRC screening uptake in rural areas [37], two Spanish studies [15, 38] did not find any association between willingness to be screened or screening uptake and the area of residence.

Married people have been shown to be more compliant with healthier behaviour advise elsewhere [39]. In a large European study carried out in UK [40], the authors found that controlling by age and educational level, married couples were more willing to take part in screening programs and presented higher attendance screening rates than those non-married. Invitations of both partners increased screening participation rates.

Lifestyle and health factors have also been associated with screening uptake. For example, current smoking habit, which has been considered as an indicator of willingness to engage in preventive health behaviour, has been associated with poor CRC screening adherence, whereas screening rates increased in studies reporting participation in former smokers [41, 42]. However, this finding has not been consistently found across the studies [15].

Inconsistent results have also been obtained regarding the effect of comorbidity on screening behavior, and, in consequence, it has been suggested that the effect of specific diseases should be studied separately [41, 43]. Health behaviours such as receiving regular checkups or having a

usual source of care have been associated with higher rates of screening uptake [15, 42]. In a nationwide US survey carried out in a representative sample of 61.068 participants aged ≥50 yr [42], routing doctor's visit in the last year was the most important predictive factor of up-to-date CRC screening in the multivariate analysis (OR 3.5, 95% CI (3.2–3.8)) regardless of the screening strategy used. Adherence to other cancer screening behaviours such as prostate cancer screening in men or breast cancer in women has also been positively associated with CRC screening uptake and specific studies have already been carried out [44, 45]. In a large survey study performed in men to investigate the effect of prostate cancer screening in CRC screening uptake [45], adherence to prostate cancer screening exerted the largest independent effect on CRC adherence regardless of the method used for screening (prostate-specific antigen or digital rectal exam) (OR 3.51, CI 95% (3.30–3.73)). Similarly, in the BRFSS, adherence with either cervical cancer or breast cancer screening in women ≥50 yr, was independent predictor of an CRC screening (OR 1.88, $P < 0.001$) [44].

2.2. Health Care System and Provider Factors. Health care providers play a key role in the screening behaviour process by increasing awareness about CRC and screening tests in participants, reducing perceived barriers and increasing perceived benefits of screening tests. Physician recommendation has shown a strong correlation with CRC screening behaviours across the studies [46–48]. For example, in a random-digit-dial survey carried out in USA involving 1002 participants ≥50 yr [48], clinician's recommendations were the most important independent predictor of up-to-date CRC screening either in participants were younger or older than 65 yr (OR 13.4, CI 95% (7.2–25) and OR 12.4 CI 95% (5.7–27.1), resp.).

In a recent national representative survey of 1266 US physicians [49], 95% and 80% routinely recommend screening colonoscopy or FOBT to asymptomatic, average-risk patients, respectively. Interestingly, the most frequent practice was to recommend two modalities (56%), with FOBT and colonoscopy being the most commonly-recommended tests (50%). In fact, fewer than 10% routinely recommend all test modalities. This aspect is of great importance as several studies have reported the preferences of average-risk population for different CRC screening tests. Unlike family-risk population for CRC, average-risk population seem to prefer noninvasive testing [50]. Therefore, the clinician's preferences for more invasive tests could be a barrier against screening. Recent evidence suggests that immunochemical FOBT could be better accepted than guaiac occult blood tests because of a lower number of tests required, the lack of dietary and drug restrictions, and easier and less unpleasant sampling methods [51, 52]. Offering available recommended strategies and discussing benefits and drawbacks with patients have been suggested as the most effective procedure to achieve high participation rates [49].

Health system factors have been associated with CRC screening uptake and physician recommendation [53, 54]. Apart from the lack of insurance previously commented, coverage for accessing to the screening service, lack of time to discuss CRC screening with the patient, or lack of physician's reminders have been consistently reported as barriers [53, 54].

2.3. Psychosocial Factors. Psychosocial factors involve those related to knowledge about CRC and screening, risk perception of CRC, and perceived barriers and benefits.

2.3.1. Knowledge about CRC and Screening. Knowledge about CRC and screening has been assessed in different ways across the studies [15, 18, 38, 55–57], including questions about risk factors for developing CRC, incidence, prognosis, age-related risk, warning signs or symptoms, and knowledge about recommended CRC screening tests. The lack of knowledge on CRC and screening has been suggested as a prominent barrier to screening adherence [15, 38]. It could be a more important barrier in areas with an opportunistic screening than in those with well-organized programs [58] and it has been reported as a major barrier among minority ethnic groups [59]. In a prospective study carried out in Spain [38], awareness of risk factors (OR 2.32, 95% CI (1.49–3.61); $P < 0.001$) and CRC signs or symptoms (OR 1.65, 95% CI (1.03–2.64); $P = 0.04$) were independent predictors for intention to participate in CRC screening. These authors reported in a later study [15] that knowledge of CRC symptoms was associated with having ever used either CRC procedures (OR 6.46, CI 95% (4.28–9.74); $P < 0.001$) or up-to-date screening (OR 7.23, CI 95% (4.36–11.98); $P < 0.001$).

The relative low public awareness about CRC in European studies contrast with data reported in US population. For example, an Irish study [60] reported that only 26% of patients with CRC could name a CRC symptom, compared with 53% and 71% for lung and breast cancer, respectively. In a recent British population-based sample, recall of cancer warning signs using an open question was less than 30% [61]. In Spain, awareness of at least one warning sign or symptom related to CRC ranged from 21% to 56%. [15, 38]. However, knowledge of CRC screening tests in some states of USA was over 80% [46].

2.3.2. Risk Perception of CRC. High-risk perception of developing CRC have been frequently associated with higher screening participation rates. For example, in one study carried out in a large representative sample of UK, participants who answered that their risk was higher than average-risk population were more willing to participate in CRC screening (98%) than those who answered same risk (84%) or lower risk (74%) [62]. In addition, unhealthy behaviours such as smoking or sedentary has been associated with a higher perception of risk [63, 64]. Similarly, the presence of bowel symptoms, comorbidity, high body mass index, and anxiety has also been associated with increased intention to participate [63, 64]. The lack of recognition of cancer risk has been suggested as a barrier of low participation in cancer screening among nonwhite groups [63]. However, the association between screening uptake and high perception

risk has not been consistently found across the studies [15, 38].

2.3.3. Benefits and Perceived Barriers against CRC Screening. Although different theoretical models have been developed in order to achieve a better understanding of health behaviour, all of them identify attitudes as important predictors of intention to screening and screening uptake. One of the most popular theoretical models is the Health Belief Model (HBM) [16]. This model theorizes on people's beliefs regarding the risk for a disease or health problem, and according to their perceptions on the benefits of taking actions to avoid it, analyzes their readiness to take action. In this way, people with negative attitudes such as embarrassment, anxiety, disinterest, fear of cancer or screening, subjective perception of pain or danger about screening, lack of time, feeling healthy, apprehensions about the bowel preparation, laxatives or insertion of a tube, and discomfort are more reluctant to participate in screening programs [18, 56, 65–67]. In a recent study performed in Spain [56], fear to CRC or to screening tests and embarrassment were the main barriers that contributed to a lower participation. This study also suggested that perceived barriers could be more important than benefits in predicting CRC screening. A recent systematic review focused on screening barriers in participants over 65 years found that the most commonly reported barriers related to screening tests were unpleasantness, discomfort, and perceived risk associated with performing tests [68]. Some studies have also suggested that barriers to screening are not homogenous across screening tests and that test-specific barriers warrant consideration in designing strategies to promote screening [69].

More barriers have been detected in minority ethnic groups such as African Americans, Asian people, or Hispanics [59, 63, 70]. A recent nationwide study focused on awareness of CRC, and attitudes to sigmoidoscopy screening carried out in UK [59] showed that the most important barrier against screening differed between white and nonwhite participants. Lack of time was the major limiting factor in white participants whereas embarrassment predominated in nonwhite invitees. Attitudes have also been shown to vary depending on socioeconomic position, with negative attitudes overrepresented in lower socioeconomic and less educated groups [18, 71].

3. Interventions to Promote CRC Screening Uptake

Interventions aimed at increasing CRC screening uptake can be classified into three categories: those that target patients, those that target providers, and those targeting health systems and communities.

3.1. Interventions Targeting Patients. The benefit of intervention targeting patients, defined as an increment in screening participation, has not always been demonstrated, probably because of the heterogeneity of the studies and several types of interventions used. Patient reminders consist of written or oral information (i.e., phone calls) reminding the necessity of undergoing screening to potential participants [72, 73]. The aim of this intervention is to schedule an appointment with the health care provider in order to demand CRC screening. In general, patient reminder-based studies have shown moderate efficacy for increasing screening uptake [72–75]. In a recent study [72], 1546 participants were randomized to a control group; a standard group (invitation letter, FOBT, and reminder letter); a tailored intervention (standard group intervention and discussion about personal barriers); or a tailored intervention and reminder phone call. One year later, screening uptake was significantly higher in those groups which received reminders compared to the control group (33% versus 46%, 44%, and 48%, resp.). It has also been suggested that the way in which screening is offered to the population may determine screening acceptance. Particularly, two randomized studies have shown that direct mailing of a FOBT kit is an efficient way to increase screening participation in the average-risk population [27, 74].

An association has been found between lack of knowledge about CRC and negative attitudes, unwillingness to participate in CRC screening, and finally screening behaviours [18, 56, 76]. Because of the positive relationship between screening uptake and knowledge about CRC and screening, several studies have assessed the impact of educational interventions focused on average-risk screening population. The purposes of these studies are increasing awareness on CRC and screening and motivating people to be screened. It has been suggested that high rates of screening uptake can be achieved by modifying the phases of the "behavior process", that is, knowledge about the most important features of CRC and screening, attitudes (reducing barriers and increasing perceived benefits), and intention to undergo screening [18, 56]. In some educational interventions participants are provided with some type of educational material including visual images or videotapes [56, 77, 78], educational leaflets [79], posters and calendars [80]. Specific interventions have been designed to increase screening uptake in minority ethnic groups [81, 82]. For example, a patient navigator, defined as a health educator trained in providing better access to healthcare services (i.e., scheduling procedures, educating patients, and explaining instructions for colonoscopy or FOBT) has been demonstrated to be useful for increasing CRC screening uptake in ethnic minority groups [82]. In general a combination of interventions may have a greatest impact on screening rates [83].

3.2. Interventions Targeting Providers. Participant's compliance is usually associated with provider's motivation [84]. The aim of the interventions targeting providers is to increase delivery of recommended cancer screening services by providers. Similarly to interventions targeting patients, it has been suggested that reducing barriers and increasing positive attitudes as well as intentions about screening would have a positive impact on screening test recommendation by providers. The desired effect is to stimulate ordering screening tests and finally to increase test completion [85]. Interventions focused on providers include: provider audit and feedback, incentives, and reminders. Regarding provider

audit and feedback interventions, medical records are usually analyzed before and after intervention to assess performance of delivering or offering screening tests to patients. A recent systematic review [86] evaluated the effect of this intervention in completion FOBT [87–89] and sigmoidoscopy [88]. Whereas the completion of FOBT screening increased 12 to 23 percentage points, no effect was found in individuals invited to screening sigmoidoscopy. The conclusion was that provider audit and feedback intervention are effective for increasing CRC screening uptake with FOBTs, but the current evidence is insufficient for other screening strategies.

Incentive interventions try to motivate providers with direct or indirect rewards (usually economic incentives) to promote CRC screening in their patients. However, these studies are scarce in the literature and poorly effective [90]. In one study [90], 52 primary care sites were randomized to the intervention or standard care. Intervention consisted of a financial award and an audit and feedback intervention. No significant differences in screening compliance were found between both groups.

Little evidence supports the efficacy of physician reminder-based interventions [91]. In one study [73], 110 physicians and 21.860 patients were randomized to receive reminders or standard care. Whereas screening rates were higher for patients who received mailings compared to those who did not (44.0% versus 38.1%, $P < 0.001$), they were similar among patients of physicians receiving electronic reminders and the standard group (41.9% versus 40.2%, $P = 0.47$).

3.3. Organizational Interventions to Improve Access. Improving the referral of patients for screening [92], delivery capacity of services for screening or patient access reducing costs for participants or identifying someone to help patients to navigate the health care system [93] has been associated with an increased screening acceptance. The development of special clinics devoted to screening, the use of planned care screening visits involving physicians and health or non-health professionals could increase screening rates reducing the barrier of physician's lack of time [83]. However, an important financial investment is necessary and it has been reported as a major barrier [94].

4. Conclusion

Underuse of population-based CRC screening is a multifactorial problem involving patients, providers, and the organizational screening process. Plausible target factors for interventions aimed at increasing compliance have been identified at different levels. Specific interventions targeting these factors have been designed to increase screening uptake. However, they have had different success across the studies depending on the screening strategy and the intervention used. Despite the efforts, the impact on screening uptake has been low or moderate. A better knowledge on factors associated with screening compliance and development of more efficient interventions are warranted in order to achieve higher rates of CRC screening uptake.

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Review Article

Fecal Molecular Markers for Colorectal Cancer Screening

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Despite multiple screening techniques, including colonoscopy, flexible sigmoidoscopy, radiological imaging, and fecal occult blood testing, colorectal cancer remains a leading cause of death. As these techniques improve, their sensitivity to detect malignant lesions is increasing; however, detection of precursor lesions remains problematic and has generated a lack of general acceptance for their widespread usage. Early detection by an accurate, noninvasive, cost-effective, simple-to-use screening technique is central to decreasing the incidence and mortality of this disease. Recent advances in the development of molecular markers in faecal specimens are encouraging for its use as a screening tool. Genetic mutations and epigenetic alterations that result from the carcinogenetic process can be detected by coprocytobiology in the colonocytes exfoliated from the lesion into the fecal matter. These markers have shown promising sensitivity and specificity in the detection of both malignant and premalignant lesions and are gaining popularity as a noninvasive technique that is representative of the entire colon. In this paper, we summarize the genetic and epigenetic fecal molecular markers that have been identified as potential targets in the screening of colorectal cancer.

1. Introduction

In Canada, despite increased awareness with improved screening techniques, colorectal cancer (CRC) remains the second leading cause of death from cancer in both men and women [1]. When detected at stage I or II, surgical cure rates approach 90% and 75%, respectively [2, 3]; however, detection is often postponed until patients become symptomatic [4], which may not occur until 2-3 years later, by which time the lesion is often of high grade [5]. As such, detection of precancerous lesions and early CRC is vital to achieving the ultimate goal of screening: decreased incidence and mortality due to CRC. The ideal screening technique should be (a) able to detect disease at a curable stage, (b) both highly sensitive and specific, (c) able to elicit a high participation rate, (d) affordable, (e) safe for the patient and the physician, (f) more beneficial than the adverse effects, and (g) easy to perform [6, 7]. Current screening techniques do not accomplish these noble goals.

Colonoscopy is currently considered the "gold standard" of CRC screening; however, despite recommendations, less than 60% of eligible individuals over the age of 50 have undergone this test [8]. Factors including patient discomfort, invasiveness, embarrassment, high cost, and considerable expertise and equipment required may all limit the appeal of this screening technique [8, 9]. Flexible sigmoidoscopy (FS) has shown promise, identifying 50–70% of advanced distal lesions [10]; however, approximately 1/3 of the neoplasms are too proximal for detection [5] and the procedure is invasive and cumbersome for patients [11]. Noninvasive method of fecal occult blood testing (FOBT) has gained popularity as a detection tool for CRC. There are two techniques for the detection of occult blood hemoglobin: (a) chemical/enzymatic FOBT by reacting with the peroxidase of the heme group, often relying on guaiac as a reagent, and (b) immunochemical/immunological FOBT that uses antibodies against human globin [12, 13]. This technique has reduced CRC mortality by 15–33% [14, 15]; however, it is limited as it (a) may detect bleeding from any site including the stomach or small bowel, (b) may falsely react with plant peroxidases or heme in red meat, and (c) can only detect actively bleeding lesions. As such, sensitivity to precursor lesions such as adenomas lies in the low 10–20% range [10]. Additionally, false-negative and false-positive

results frequently occur. As such, a screening technique that combines high sensitivity and specificity for adenomas and early-stage cancer, minimal invasiveness, safety, affordability, and acceptability by patients and physicians is required [16]. One of the significant advantages of colonoscopy is that, in addition to detecting the malignant tumours, adenomas and other benign precursor lesions can be detected and removed. This will not only reduce the mortality from colorectal carcinoma but also decrease the incidence of this disease. This is a noteworthy advantage in comparison with FOBT that cannot effectively reduce the incidence of colorectal disease.

In 1989 it was first observed that viable gastrointestinal cells could be recovered from human stools and thus began the science of coprocytobiology [17]. Since then, the understanding of the natural history of CRC and its carcinogenic pathway has improved. With this increased understanding it is expected, therefore, that this improved knowledge should translate to better screening techniques that are more accurate and acceptable while minimizing their invasiveness [5]. Detection of molecular markers in fecal specimens is a promising screening technique. This noninvasive test has shown higher levels of specificity and sensitivity for the detection of precancerous and cancerous colorectal lesions and is associated with greater patient compliance. It has additionally been suggested that sensitivity rates of many of these molecular markers may increase with repeated testing within a well-defined screening program [18, 19]. The continued evolution in the studies of genomics, transcriptomics, proteomics, and metabolomics allows for the continued identification of potential cost-effective, safe, and simple molecular markers [20]. Comparisons between these tests can be difficult due to differences in methodologies and study populations [18]. In this paper, we summarize the single- and multipanel molecular markers that have been described in the recent literature.

2. Materials and Methods

Using PubMed and Google Scholar, an English literature search was performed using the text phrases "colorectal" and "molecular marker" published within the past 10 years (since 2000). Articles were restricted to fecal/stool specimens. The PubMed search listed 85 articles while the Google Scholar listed 6470 entries. The PubMed "Related Articles" feature identified an additional 45 relevant articles. Reference lists from these manuscripts were reviewed, and secondary articles were read and analyzed. Articles chosen were limited to fecal genetic and epigenetic markers. A total of approximately 150 articles were read, and 87 of these were finally included in this paper. We begin this paper with a brief introduction of the current understanding of carcinogenesis pathways in the development of CRC.

3. Development of CRC

An understanding of the carcinogenic pathway leading to the development of CRC is necessary to comprehend the use of molecular markers as a screening tool. As in the general population the majority of cancers (85%) are sporadic [6], and early identification of precursor lesions may provide the opportunity to intervene in the carcinogenic process at a curable stage. Early detection is central to decreasing mortality and morbidity. These malignancies are believed to develop due to an accumulation of mutations in oncogenes, tumour suppressor genes, and DNA mismatch repair genes [21]. Traditionally, three separate pathways in the development of CRC have been described.

(i) *The Chromosomal Instability Pathway* is the most common sequence in the development of CRC, caused by whole or partial chromosomal loss/mutation [22]. It is hypothesized that a step-wise accumulation of mutations in a variety of genes, including oncogenes and tumour suppressor genes, results in abnormal cells that have a greater propensity for proliferation and growth [6]. The proposed process, with genes typically implicated, includes sporadic mutation in one allele of a gene (proposed *APC* gene on chromosome 5q) that results in the formation of dysplastic crypts [23, 24]. Genomic instability incurs a growth advantage to mutated cell lines permitting clonal expansion [10]. Mutation to the *K-ras* gene on chromosome 12 causes progression from an early-type adenoma to an intermediate- and then late-type adenoma. Mutations to *DCC* gene on chromosome 18 may enhance cell growth and spread. Finally, a *TP53* mutation on chromosome 17p in large adenomas with severe dysplasia promotes conversion to a carcinoma [22, 23]. It has been additionally suggested that hyperplastic polyps, like adenomas, may develop into cancerous lesions through a similar step-wise progression [25] via a serrated adenoma intermediate [26]. Serrated adenomas and serrated hyperplastic polyps are reported to have high rates of microsatellite instability and lower rates of mutations in *APC, p53*, and *K-ras* [27]. It is suggested that 20–30% of CRCs are derived from serrated polyps rather than adenomas. These occur in a more elderly population, are frequently right sided, endoscopically less obvious, and have a faster growth potential [7].

(ii) *The microsatellite instability pathway* appears to occur in 12–15% of all CRCs. In these patients, a loss of the DNA mismatch repair system results predominantly in mutations to large poly-A-regions (big adenine tracts—BAT) and CA-repeats [10]. Additionally, resulting mutations from inactivation of this system could affect all microsatellites, not only BAT and CA-repeats. This pathway is explained further in Section 7.1.

(iii) *The third pattern of development of CRC* includes the 2-3% that do not fit into the above two categories [10]. The epigenetic process of methylation of the promoter regions of genes is common in neoplasia and causes silencing of the gene, that is, being "turned

off" [22]. As such, methylation of tumour suppressor genes may promote the development of cellular proliferation and lead to tumour development. Methylation of CpG islands is one of the primary epigenetic changes involved in the pathogenesis of CRC that is detectable in fecal specimens [2]. Two of these methylation pathways of CRC include those with rare methylation (CIMP−) and those with aberrant methylation of multiple genes (CIMP+). This is further explained in Section 7.3 under the "Epigenetic Changes."

The events of these pathways transpire over an extended period of time, with conservative estimates of 5–10 years being required for the development of CRC [26]. This interval therefore provides a window of opportunity to detect the adenomatous or early CRC lesions while still at an early curable stage. Determining which adenomas will become carcinomatous can be difficult, as over 50% of individuals will develop adenomatous lesions over their lifetime while only 6% will have malignant transformations [7]. Differentiation between these two lesions to identify and remove precancerous polyps is a key feature of the optimal screening exam to prevent CRC-related death [28]. Certain characteristics infer a greater risk of progression. Factors including severe dysplasia, a villous histological type, large size (≥ 1 cm), and the patient's age are risk indicators of potential malignant transformation [26, 28]. Identification of these features in an adenomatous polyp and its subsequent removal may reduce the incidence of CRC and mortality in high-risk groups [29]. Though many molecular tests have achieved a relatively high sensitivity for cancerous lesions, tests to detect precancerous lesions such as high-risk adenomas have not been adequately studied [20]. Further, current screening continues to be ineffective, as only 37% of CRCs are diagnosed while the cancer is localized. Such inefficiencies in screening may be due to suboptimal sensitivities, low patient acceptability, or high resource demands that limit availability [29].

4. Molecular Markers

The ideal biomarker for the detection of CRC and premalignant lesions would be (a) consistently positive in the presence of "screen-relevant neoplasia" and negative in the absence, (b) stable despite fecal toxicities, (c) easily recoverable from the stool, and (d) reproducibly assayed [30]. The multiple genetic events associated with the development of CRC coupled with the long-time interval between the initial adenomatous/polypoid event and the cancerous lesion suggest a role for molecular markers in early detection. These specific changes occurring within the DNA, RNA, and proteins may potentially serve as biomarkers and be used as screening, diagnosis, and as predictive and prognostic markers in CRC. These genetic alterations may be due to gene mutations, gene amplification, aberrant DNA methylation, or chromatin modifications [20]. The ultimate goal of the use of molecular markers is a biomarker panel to detect carriers of early CRC or precursor lesions in order to reduce the incidence and mortality of this highly prevalent cancer. Molecular markers must be both highly sensitive and specific. Methylation of markers such as estrogen-receptor and insulin-like growth factor II may be detected in patients with CRC; however, such methylation is additionally common in aging colon and is thus an unattractive marker [15]. An effective marker for detection should be regularly released from the tumour/precancerous lesion, withstand metabolic degradation, and be readily retrievable and measurable from the medium collected [7].

Such markers may be found directly in the tissue; however, retrieval requires an invasive procedure. More recently, assays have been developed that detect genetic materials shed from CRC into faecal specimens. Sidransky et al., in 1992, were the first to use fecal samples to detect CRC by testing for mutations in the *K-ras* gene [31]. Over the past thirty years, a wide array of single genetic and epigenetic changes that are detectable within fecal samples have been identified. Concurrently, multimarker panels have been proposed. The first multimarker panel was published eight years later (2000) when Ahlquist et al. published a trial with 15 point-mutations on *K-ras, p53, APC, BAT-26* and long-DNA (L-DNA) [32]. Many of the single and multi-panel genes that have been identified as potential molecular markers are herein summarized.

5. The Process of Fecal-Based DNA Testing

Colonocytes that are present on the surface of the colonic mucosa are continuously shed into the lumen of the colon and excreted as a normal component of stool [6, 17]. These cells are shed from the lower crypts at a rate of at least 10^{10} cells per day, each with a lifespan of 3-4 days [33]. The renewal turnover is 1% per hour, and within four days the entire colonic mucosa is renewed [5]. In the 19th century it was first observed that exfoliated cells in colonic washings could be used for the diagnosis of CRC. Current advances in coprocytobiology [17] understand that, in the normal colon, exfoliation is triggered by apoptosis or anoikis (involution) when separated from the basement membrane. In malignant lesions, however, genetic and/or epigenetic changes prevent this destruction of colonocytes, allowing them to survive within the stool. This may be due to increased cellular proliferation or reduced cell-cell or cell-basement membrane adhesions [7]. Additionally, the number of colonocytes exfoliated from malignant lesions is 4-5-fold greater than from normal tissue [5]. As such, tumour markers present within these cells are preserved. Within the stool are bile acids and cytolytic compounds that may lyse colonocytes and expose the DNA to metabolically active microflora and fecal proteases that may destroy the material and catabolize potential tumour markers [7]. To prevent this natural occurrence, the addition of a DNA-stabilizing buffer immediately afterdefecation has been reported to prevent DNA degradation for several days [34]. DNAase inhibitors in these buffers prevent degradation during transportation and storage of these specimens until they can be examined [7]. The somatic cell sampling and recovery (SCSR) process involves the isolation of exfoliated colonocytes from a small

sample of stool that can be collected and transported in a unique medium at suitable temperatures to provide cells for the detection of a number of biomarkers [17]. Such cells with mutations in key genes or alterations in protein products can then be analyzed with molecular biology or biochemical techniques [21].

To begin the analysis, abnormal genetic material must then be separated from normal human DNA and bacterial DNA prior to amplification and testing for molecular markers [29]. Human genetic material within fecal specimens is sparse, with a median concentration of 309 ng/g stool (ranging 5–21 115 ng/g stool) [35]. This accounts for only 0.01% of the total genetic material in DNA, the remaining portion including genetic materials from colorectal microbial flora, eukaryotic parasites, and undigested dietary remains [7]. As such, materials recovered from stool must be enriched to retrieve gene sequences for PCR analysis. After amplification genetic molecular markers can be detected. The wide variety of methodologies for the detection of these markers is beyond the scope of this paper and will not be discussed.

A study examining the optimal number of fecal specimens for molecular screening exams found no additional benefit for more than one specimen per patient, with a 93% concordance between the initial results and all subsequent analyses as no additional mutations were detected on second or third screenings [36]. Due to the heterogeneity of fecal matter, it is, however, important that screening includes samples from the entire stool. Depending on the site of the lesion, markers may be present in different parts of the stool, as left-sided tumours tend to have markers represented on the surface whereas in the unformed feces from right colon colonocytes may be found throughout the sample [7].

6. Single Genetic Markers

The four most commonly studied genes for faecal CRC include the *KRAS, TP53, APC,* and *DCC* genes. Detection of *DCC* mutations in fecal specimens is not well studied; however, *KRAS, TP53,* and *APC* are well reported in the English literature, as, for example, Calistri's study reports that *K-ras* and *p53* were equally altered in 35% of CRC patients and *APC* mutations were reported in 13% [37]. These genes are now discussed in detail.

6.1. KRAS Gene. The *KRAS* gene is located on the short arm of chromosome 12 and encodes the *K-ras*guanosine-triphosphate- (GTP-) binding protein with a role in signal transduction for regulation of proliferation and differentiation [6]. Normally the *K-ras* protein hydrolyzes GTP, thereby inactivating the ras protein [6, 38]. This was the first molecular marker to be studied in fecal specimens nearly 30 years ago [31]. Mutations to this gene are more common in lesions of the distal colon [18]. Activating mutations of *KRAS* may result in uncontrolled cellular proliferation and resistance to EGFR-targeted therapies [39]. Only one copy of this gene needs to be mutated to cause uncontrolled cell growth, as *K-ras* is a signal transducer [38]. The majority (70–80%) of these mutations are on codon 12, although they may occur on codons 13 and 61. With fecal specimens, *K-ras* mutations have been detected in 35–42% of CRCs and approximately 50% of adenomas larger than 1 cm [6]. This marker remains nonspecific as it has been detected in stool from morphologically normal colonic mucosa, self-limiting hyperplastic polyps, and nondysplastic aberrant crypt foci [15]. Additionally, this marker is nonspecific for CRC, as its fecal presence may be positive in benign, unrelated pathology such as pancreatic hyperplasia [5]. Table 1 summarizes the sensitivity and specificity of *KRAS* studies as available in the reviewed literature which are briefly discussed below.

(i) Zhang et al. (2011) [39]. A chip-based temperature gradient capillary electrophoresis (TGCE) technique was used to detect mutations in *K-ras* among stool specimens from 30 CRC patients and 15 normal-controls. A total of 17/30 CRC patients demonstrated *K-ras* mutations (57%), and only 1/15 controls had the mutation, thus yielding a specificity of 93%.

(ii) Chien et al. (2007) [40]. This study explored the role of this molecular marker in the identification of CRC. *K-ras* codon 12 mutations were identified using reverse transcription-polymerase chain reaction (RT-PCR) and amplified restricted fragment length polymorphism analysis, feces from 5% of "normal" control, and 41% of CRCs. These mutations were significantly associated with a younger patient age.

(iii) Øgreid and Hamre (2007) [27]. In this paper, *K-ras* mutations were detected in a stool sample 18 months prior to its endoscopic identification.

(iv) Rengucci et al. (2001) [41]. Stool specimens retrieved from 46 patients with CRC showed 6 to be positive for *K-ras* mutations: 2 in exon 2 and 4 in exon 1. One-third of tissue samples were positive for this mutation.

(v) Notarnicola et al. (2000) [42]. K-ras mutations were detected in fecal samples from 26 CRC patients using PCR amplification and restriction enzyme analysis. Fecal *K-ras* mutations were detected in 26.9% of cases.

(vi) Smith-Ravin et al. (1995) [43]. 11 patients with sporadic CRC provided stool samples to be analyzed for the *ras* mutation with a nonradioactive, allele-specific mismatch method. Approximately half of the stool samples were positive for the mutation.

The use of the *KRAS* gene as a molecular marker has not been supported in CRC screening by several studies [44, 45]. Though this gene can detect some individuals with CRC, it is often ineffective at identifying individuals who are at an increased risk of developing this cancer based on preneoplastic lesions. It is not associated with risk factors or with the identification of high-risk individuals [44]. This marker is a common component of multitargeted assays, as described later.

Table 1: Studies of *KRAS* genetic alterations in fecal samples.

Authors and reference	Technique	Specimen	Specimen n =	Control n =	Sensitivity	Specificity
Zhang et al. [39]	Chip-based temperature gradient capillary electrophoresis (TGCE)	CRC	30	15	57%	93%
Chien et al. [40]	RT-PCR + amplified restricted fragment length polymorphism analysis	CRC	29	20	41%	95%
Rengucci et al. [41]	Denaturing gradient gel electrophoresis	CRC	46	18	33%	100%
Notarnicola et al. [42]	PCR amplification and restriction enzyme analysis	CRC	26	None	26.9%	NA
Smith-Ravin et al. [43]	PCR amplification using allele-specific mismatch method	CRC	11	None	50%	NA

6.2. TP53 Gene. As elucidated in the adenoma-carcinoma pathway, mutations in the gene *TP53* most commonly occur in the later stages of CRC. This gene is located on the short arm of chromosome 17 and encodes the gene p53, a well-studied player in many forms of human carcinogenesis. Mutations may occur at exons 5, 6, 7, or 8 [6, 45]. At mutation, the p53 protein is deregulated, resulting in an increased genomic instability and malignant progression. On fecal screening, such mutations have been identified in 50–70% of CRCs [5], up to 64% of severely dysplastic polyps [10], and 4–26% of adenomas [6]. Conflicting results regarding the detection rate of this mutation exists in the literature as seen below.

(i) Rengucci et al. (2001) [41]. Stool and tissue samples were received from 46 patients with CRC. Though in 37% of tissue samples ($n = 17$) this marker was present, in fecal samples only 3 patients had mutations, two found on exon 6 and one in exon 8.

(ii) Notarnicola et al. (2000) [42]. p53 mutations were detected in fecal samples from 26 CRC patients using PCR amplification and single-strand conformation polymorphism. Mutations were detected in 50% of cases.

6.3. APC Gene. The *adenomatous polyposis coli* (*APC*) gene is found on chromosome 5q21 and encodes the APC "gatekeeper" protein that is responsible for the regulation of β-catenin, an inductor of growth-promoting genes in the *Wnt* signalling pathway [6]. Additional roles of APC include regulation of cell adhesion, interaction with microtubules for cell migration, and blockage of cell cycle [46] Mutations to the *APC* gene occur early in the adenoma-carcinoma sequence and in fecal screening are reported to be detected in 20–82% of adenomas and 52–60% of CRCs [6]. Unlike *KRAS* and *TP53*, mutations are not limited to a small region and can occur anywhere along the first 1600 codons of the gene, [5] though 83% occur within the first part of the sequence [10]. Such mutations occur in both inherited and sporadic forms of CRC [12]. A sample of the results of detection of this marker in a couple of studies are listed below.

(i) Suceveanu et al. (2008) [47]. In this study ($n = 200$), 15 exons of the *APC* gene were analyzed for mutations, which were identified in exons 4 (9 patients), 9 (1 patient), 13 (6 patients), and 15c (5 patients) with none occurring in exons 5, 7, 8, 10, 12, and 15.

(ii) Traverso et al. (2002) [48]. DNA was purified from stool samples of 28 patients with CRC, 18 with adenoma (≥ 1 cm), and 28 normal-controls. Samples were screened for *APC* mutations with digital protein truncation. Mutations were present in 57% patients with neoplasia (26/46) and in none of the controls.

6.4. Additional Gene Mutations. Additional gene mutations in fecal specimens that have been explored in the literature include the following.

(i) DCC. The deleted in colon cancer (*DCC*) gene is found on the long arm of chromosome 18 and under normal circumstances maintains cell-cell adhesions. Though well-studied in tissue specimens, its expression in faecal samples remains poorly researched and understood. In one study, on fecal analysis, mutations were reported in 70% of CRCs, 11–13% of small adenomas, and up to 60% of adenomas with malignant foci enhancing cell growth and metastatic spread [6]. Further research in this area is required to elucidate the potential role of *DCC* as a molecular marker.

(ii) RPL19 [49]. The gene *RPL19* is responsible for encoding the ribosomal protein L19. In a study of fecal matter from 44 CRC patients, 15 controls, and 11 colonic cell lines, a quantitative real-time reverse transcription PCR detected 7/24 patients with late-stage CRC expressed 2-times more RPL19 in colonic tumour tissue than normal, and the mean

fecal RPL19 mRNA levels of late-staged patients were also higher than the controls. The authors concluded that the RPL19 protein is associated with increased expression in advanced CRC patients and this is detectable in fecal matter.

(iii) COL11A1 [47]. The COL11A1 gene encodes the collagen α-1 chain protein. Mutations to this gene in CRC are not well studied in the feces. In Suceveanu's study ($n = 200$), fecal samples underwent denaturing gradient polyacrylamide gel electrophoresis. Exons 16, 38, 41, 54, 55, 56, and 57 were studied. In exons 16, 38, and 41 no mutations were detected; however, a displaced band pattern was detected in 6 cases for the exons 54, 55, 56, and 57.

(iv) COX-2, Matrix-Metalloproteinase-7 mRNA [7]. Fecal analysis of mutated COX-2 yielded a specificity of 100% and sensitivity of 87%. Analysis of matrix metalloproteinase-7 mRNA was detected in 65% of patients. 90% of CRCs can be detected by these two markers combined.

(v) C-myc p64, c-myc p67, and c-erbB2 [50]. Colonocytes were isolated in stool samples from 15 patients with CRC and 15 normal-controls, and using reverse transcriptase PCR the expressions of c-myc p64, c-myc p67, and c-erbb-2 were evaluated separately and in combination. C-myc p64 was expressed in 78.5% of CRC patients and only 13.3% of the control (sensitivity 86.7%). C-myc p67 was detected in 78.6% of CRC patients and 13.3% of controls (sensitivity 86.7%), and c-erbb-2 showed no significant difference in mRNA expression between CRC and controls. In a panel combination assay, a sensitivity of 64% was found, with 100% specificity.

7. Introduction to Epigenetic Changes

7.1. Fecal Microsatellite Instability. Microsatellite instability (MSI) occurs when short stretches of DNA sequences with a tandem repeating pattern (a microsatellite) undergo a change in length due to a loss of function of at least one of the six mismatch repair genes (*MLH1, MSH2, PMS1 PMS2, MSH3, MSH6)* resulting in an accumulation of mutations and errors of replication causing lengthening or shortening of the microsatellite [6, 12, 22]. These errors in replication can be identified with microsatellite marker alleles, nucleotide sequences present in tumour DNA but absent from normal genetic material [46]. In sporadic CRC, MSI is most often associated with epigenetic silencing of the mismatch repair gene *MLH1* [12]. MSI commonly affects genes with microsatellites in their coding region [22]. This instability is commonly detected in patients with hereditary nonpolyposis CRC (>90% in CRCs and 80% adenomas), but less frequent in sporadic CRCs (15%) and adenomas (5%) [5, 22]. MSI has been shown to confer a better prognosis compared to stage-matched stable tumours [12]. The most common fecal marker of MSI used is Big Adenine Tract-26 (*BAT-26*), a locus of 26 repeated adenine nucleotides located in the *MSH-2* mismatch repair gene [5, 22, 24]. Among right-sided cancers proximal to the splenic flexure, BAT-26 is a feature in 30–40% [45]. This fecal marker alone has a sensitivity of 40% for proximal CRCs [5], and is more commonly used as part of a multitarget panel.

7.2. Long DNA. Long DNAs (L-DNA) are genetic sequences as long as 1800–2400 base pairs that can be identified in faecal specimens and used to detect CRC [6]. By corpocytobiology techniques [17], in colonocytes exfoliated into the lumen from "normal" colon, nuclear endonucleases are activated during apoptosis, disintegrating cellular DNA into fragments of 180–200 base pair. In CRC, cells are nonapoptotic; therefore, when they are shed from the tumour, they are not subjected to this degeneration and can be retrieved from stool samples [22]. Using the fluorescence L-DNA method, authors have amplified stool DNA and found that the average value for CRC was 64 ng (range 0–731 ng) compared to 0 ng (range 0–246 ng) in the healthy control. This study further found that, with a cut-off value of 25 ng, sensitivity of 79% and specificity of 89% could be achieved in fecal testing [51]. This is in concordance with another study that purified DNA from stool samples and found DNA fragments from patients with CRC to have a higher molecular weight than those from the control (>18/24 possible bands detected) [52]. In terms of its use as a fecal screening tool, L-DNA is often unstable during storage; however, the addition of a buffer with a DNAase inhibitor appears to remedy this problem. This was explored by Zou et al. using a real-time *Alu* PCR assay for quantifying faecal L-DNA. The authors found an average 75% drop in L-DNA levels in nonbuffered fecal specimens within the first day, yet, with the addition of an EDTA buffer, the integrity of the DNA was preserved. L-DNA is not specific for CRC, as its presence in stool specimens may be due to cancer of the upper gastrointestinal tract or from inflammatory bowel disease [53]. In Abbaszadegan's study, L-DNA was detected in 64% of stool samples from patients with CRC ($n = 45$) with a specificity of 95% (control $n = 20$) [54].

7.3. Methylation Markers. One of the primary epigenetic changes involved in the pathogenesis of CRC that can be detected in fecal specimens is the methylation of CpG islands [2]. CRC can be divided into two subtypes: those with rare methylation (termed CIMP−) and those with aberrant methylation of multiple genes (CIMP+). CIMP or "CpG island methylator phenotype" is increasingly recognized as a clinically and etiologically distinct group with its own epidemiology, histology, and molecular features. CIMP-positive CRCs commonly have a more frequently mutated *K-ras* gene but fewer mutations to *TP53* [55–57].

In this process, a methyl group is enzymatically transferred from the methyl donor S-adenosylmethionine to the carbon-5 position of the cytosine [26]. Hypermethylation of these cytosine residues is responsible for their transcriptional inactivation [58]. They are often identified within untranslated first exons or the promoter regions of genes responsible for regulating cellular proliferation, apoptosis, and DNA repair [2, 29]. Though there may be hundreds of hypermethylated genes, only a select few play a significantly

functional role in the development of CRC and therefore are potential molecular markers [29].

By using methyl-binding domain protein columns to capture methylated DNA, sensitivity has been shown to be markedly increased without negatively affecting specificity [59]. Detection of genetic mutations can be challenging, as a single gene can be mutationally inactivated through multiple mechanisms or mutated at varying positions. By contrast, in hypermethylation, it is often identical residues in the regulatory regions of the particular gene that are targeted by cancers, thus facilitating screening test design [60]. DNA methylation patterns have been detected during early stages of tumourigenesis at the same or greater frequency as genetic mutations. In the majority of CRC's, specific methylated genes are attractive candidates for molecular detection in stool samples [7]. Some authors have suggested that the high cost and relatively low sensitivity associated with detection of DNA mutations preclude its usefulness in population-based testing; however, methylation-based testing has been suggested to be sensitive in the detection of CRC and an increasing number of specific markers representing epigenetic signatures are being identified. Such fecal markers are attractive screening tools due to their high prevalence in early-stage neoplasia and predictability as assay targets on gene promoter regions [35]. These fecal screening tests may additionally be used as early disease markers, prognostic indicators, and predictors of therapy response [61]. Genome-wide analyses for the identification of epigenetic target genes have provided an extensive list of marker candidates, from which a large number have been studied in detail in fecal samples [11].

8. Single Epigenetic Markers

8.1. SFRP2. The *SFRP2* gene is responsible for encoding the secreted frizzled-related protein 2 (SFRP2). It is one of the *SFRP* tumour suppressor genes responsible for glycoprotein secretion to inhibit the Wnt tumourigenic pathway [62]. As such, when *SFRP* genes are silenced, the Wnt/β-catenin signalling pathway is activated. This gene contains a region rich in cysteine residues that can be methylated in CRC, and thus used as a fecal molecular marker. Hypermethylation of this gene in stool-based screening has been detected in 77–90% of CRCs with amplifiable DNA. Specificity is lacking as 23% of the "healthy" controls were found to have methylation at this locus as well. This might be explained by the understanding that foci of premalignant aberrant crypts, which are undetectable on a routine colonoscopy, may be hypermethylated at this site [15]. A number of studies have investigated the methylation of this gene as a potential fecal molecular marker. The summarized results of the sensitivity and specificity of some of these studies are in Table 2 and briefly discussed below.

(i) Tang et al. (2011) [63]. Stool, serum, and tissue samples from 169 CRC patients, 63 with advanced adenoma, 46 with nonadenomatous polyps, and 30 "normals" were retrieved and human DNA was analyzed with MS-PCR to detect methylation of *SFRP2*. In CRCs, the sensitivity of tissue analysis was the highest (88.2%) followed closely by stool (84%) and serum DNA (66.9%). Methylation of *SFRP* was less pronounced in adenomas, with sensitivities at 65.1%, 46%, and 6.4%, respectively. For the controls/normal, detection was low, at 0%, 6.7%, and 0% in tissue, stool, and serum. Overall the specificity of this marker in tissue samples was 34.9%, in stool was 54%, and in serum was 93.7%.

(ii) Wang and Tang (2008) [64]. Patients with CRC ($n = 69$), adenoma ≥ 1 cm ($n = 34$), hyperplastic polyps ($n = 26$), and "normal" ($n = 30$) provided stool and tissue samples. Fluorescence-based real-time PCR was used to analyze the *SFRP2* gene with clinicopathological correlation. Sensitivity of fecal specimens was 87.0% (60/69) for CRC, 61.8% (21/34) for adenoma, and 42.3% (11/26) for hyperplastic polyps. Two "normal" patients had hypermethylation of *SFRP2* in their fecal specimens. Hypermethylation of this gene was not significantly associated with sex, age, tumour stage, site, lymph node status, or histological grade.

(iii) Oberwalder et al. (2008) [26]. Methylation status by MethyLight was compared between patients with colorectal polyps and those with a negative colonoscopy. None of the healthy controls were found to have methylation of this gene. 33% of hyperplastic polyps and 46% of adenomas were positive for methylation. These authors concluded that *SFRP2* was the most sensitive fecal-based single DNA-based molecular marker for the identification of CRC.

(iv) Huang et al. (2007) [62]. Methylation of *SFRP2* was detected in 94.2%, 52.4%, 37.5%, and 16.7% of patients with CRC, adenoma, hyperplastic polyps, and ulcerative colitis, respectively. In the control, "healthy" subjects, only 1/24 stool analyses revealed methylation of this gene.

(v) Müller et al. (2004) [65]. A sensitivity of 90% and a specificity of 77% were reported for *SFRP2* in this study individually examining the methylation status of 44 genes. When repeated in a fecal DNA-independent test set ($n = 26$), a sensitivity and specificity of both 77% were found. The authors concluded methylation of *SFRP2* to be a sensitive single DNA-based marker to identify CRC.

8.2. Vimentin. The *Vimentin* gene is responsible for coding an intermediate filament protein constituent that normally is not expressed in colonic epithelium [2]. Normally *Vimentin* is expressed in mesenchymal-derived cells including fibroblasts, macrophages, smooth muscle cells, and endothelial cells [66]. This gene is usually neither methylated nor transcriptionally active in normal epithelial crypt cells [55]. A total of only 4 ng of human DNA is required within a fecal specimen for the detection of methylated *Vimentin* when captured using methyl-binding domain (MBD) protein and chelating the protein into a nickel-agarose matrix in a chromatography column [35]. The following studies highlight the usefulness of this fecal marker.

Table 2: Studies of *SFRP2* genetic alterations in fecal samples.

Authors and references	Technique	Specimen	Specimen *n* =	Control *n* =	Sensitivity	Specificity
Tang et al. [63]	MS-PCR	CRC Adenoma	169 63	30	84% 46%	54%
Wang and Tang [64]	Fluorescence-based RT-PCR	CRC Adenoma	69 34	30	87.0% 61.8%	93.3%
Oberwalder et al. [26]	MethyLight analysis	Adenoma	13	6	46%	100%
Huang et al. [62]	MS-PCR	CRC Adenoma	52 21	24	94.2% 52.4%	95.8%
Müller et al. [65]	MethyLight analysis	CRC	13	13	77%	77%

(i) Ned et al. (2011) [66]. A commercially available fecal DNA test named *ColoSure* has been developed that detects methylation of the *Vimentin* gene. There remains no published data on the sensitivity or specificity of this test.

(ii) Baek et al. (2009) [29]. 60 individuals with CRC, 52 with adenomas, and 37 normal-controls were investigated for *Vimentin* methylation using methylation-specific PCR (MS-PCR) with specially designed primers. A sensitivity of 38.3% for CRC and 15.4% for adenomas was found.

(iii) Itzkowitz et al. (2007) [34]. In the buffered stool samples from 40 patients with CRC and 122 normal-controls, these authors found that detection of *Vimentin* methylation alone resulted in 72.5% sensitivity and 86.9% specificity.

(iv) Chen et al. (2005) [2]. A study focusing on fecal detection of *Vimentin* hypermethylation was conducted using MS-PCR in 94 patients with CRC and 198 normal-controls. This study used MS-PCR to determine that the methylation status of vimentin exon 1 in fecal DNA from CRC patients and "healthy" controls was compared. An overall sensitivity of 46% was documented (43/94) and specificity of 90% (10% of fecal DNA samples from the control were positive for vimentin methylation).

8.3. MGMT, MLH-1, and CDKN2A. The genes *MGMT, MLH-1* and *CKDN2A* have been proposed as potential fecal molecular markers. In one study, stool from "healthy" ($n = 37$), adenomas ($n = 52$), and CRC ($n = 60$) was investigated for methylation of *methylguanine DNA methyltransferase (MGMT)* and *human mut I homolog-1 (hMLH-1)*. Methylation was detected in fecal samples from 51.7% and 30.0% of those with CRC and 36% and 11% of those with adenomas. With the addition of *Vimentin* methylation detection, a combined sensitivity for CRC was 75%, adenoma was 59.6%, and a specificity was 86.5% [29].

A second study assessed the methylation status of *MGMT, MLH-1,* and *CDKN2A* in colonic adenomas and hyperplastic polyps. The *MGMT, CDKN2A*, and *MLH-1* genes were methylated in 48%, 31%, and 0% of adenomas and 16%, 27%, and 10% of those with no detectable pathologies. Tubulovillous and villous adenomas were more frequently methylated compared with tubular adenomas. Adenomas with at least one methylation were typically larger than lesions without methylation (15.6 mm versus 7.0 mm). These findings suggest that hypermethylation of these genes may contribute to progression of polyps to carcinoma [25].

Additional epigenetic alterations that have been explored in the literature include the following.

(i) 2q14.2 (EN1, SCTR, INHBB) [61]. The gene *2q14.2* harbours three CpG islands that have been associated with the promoter region of this gene: EN1, SCTR, and INHBB. In a study examining the extent of long-range epigenetic silencing of this gene, at least one of these three CpG islands were methylated in 90% of CRCs. The most commonly methylated promoter region was EN1, with silencing observed in 73% of CRCs and 40% of adenomas. SCTR was also associated with high levels of methylation in carcinoma (53%) and adenoma (33%). Methylation of INHBB was low, detected in only 25% of CRCs and in none of the adenomatous patients. EN1 and INHBB were suggested to be associated with a poorer prognosis in early-stage CRC; however, further investigation was suggested. Bisulfite treatment with melting curve analysis from stool DNA was then used to detect methylated EN1, and a 27% overall sensitivity and 97% specificity were found. The authors concluded that epigenetic suppression of the gene *2q14.2* is frequent in CRC, and hypermethylation was suggested to be a secondary occurrence.

(ii) ITGA4 [67]. In a genome-wide search using a microarray-based assay for methylated genes, *ITGA4* was identified in 75% of adenomas of the colon and 92% of CRCs with a diagnostic specificity of 79%. As such, the authors concluded that *ITGA4* is a potential fecal DNA-based early-detection marker for CRC.

(iii) GATA4 and GATA5 [59]. The transcriptional factors GATA-4 and GATA-5 are encoded by the genes *GATA4* and *GATA5*, respectively. In the normal body, these transcription factors are essential to the normal development of the gastrointestinal tract and in the evolution of CRC. Hypermethylation of this gene resulting in loss of expression has been documented in primary colorectal, gastric, esophageal, lung, ovarian, and pancreatic cancers. When compared to other genes such as *APC, p14, MGMT, HLTF, p16*, and *RASSFIA*, methylation of *GATA4/5* confers a higher sensitivity and

specificity, respectively. *GATA4* methylation is more common than *GATA5*. Fecal DNA from two independent series of CRC patients ($n = 28$ CRC, $n = 45$ control) revealed a *GATA4* sensitivity of 51–71% and a specificity of 84–93%. As such, it was concluded that *GATA4* is a potential molecular marker for CRC screening. Hypermethylation of *GATA4/5* was not significantly associated with tumour-node metastases, stage, tumour location, sex, age at diagnosis, histologic type, or the tumour grade.

(iv) HIC1 [15]. The *HIC1* gene encodes the protein hypermethylated-in-cancer-1 (HIC1). The promoter of this gene, localized on chromosome 17p13.3 is often methylated in CRC, but not in aging or normal colonic tissue. Fecal screening for CRC with hypermethylated *HIC1* gene detection compared with FOBT has shown promising results for this epigenetic marker in 26 patients with CRC, 13 with adenoma (≥ 1 cm), 9 with hyperplastic polyps, 9 with chronic inflammatory bowel disease, and 32 normal-controls. Methylated *HIC1* promoter DNA was not detected in any of the fecal specimens from "normal" or hyperplastic polyps. Specificity was 98%. 42% of CRC-derived samples and 31% from colorectal adenoma were positive for this marker, slightly higher than the sensitivity commonly reported for FOBT.

(v) miR-34b/c and miR-148a [68]. MicroRNAs (miRNAs) are noncoding RNAs approximately 22 nucleotides in length responsible for modulation of posttranscriptional activity, targeting mRNA for inhibiting gene expression. *miRNA* genes are believed to play a major role in cancer cell biology, as hypermethylation is thought to drive initiation and progression of polyps towards CRC. Investigation of hypermethylation of miR-34b/c and miR-148a in CRC has been investigated with 5-aza-2′deoxycytidine and MS-PCR. 28 patients with CRC, 12 with high-grade dysplasia, and 39 normal-controls were studied. Hypermethylation of miR-34b/c was identified in 75% of CRC fecal specimens and 16% of high-grade dysplastic polyps. For miR-148a, a trend towards the female sex, an older age, and a decreased overall survival were found associated with these epigenetic changes.

(vi) OSMR [69]. Oncostatin M receptor-β (*OSMR*) is a receptor for oncostatin M, a member of the interleukin-6 cytokine family that is shown to inhibit a wide variety of carcinomas by inhibiting cellular proliferation. Results have shown that methylation of *OSMR* was detected in the stools of in 26/69 CRC patients (sensitivity of 38%) with a specificity of 95% (77/81). A statistically significant difference was noted between CRC patients and the controls. For Stage II CRC, 56% of stool specimens demonstrated *OSMR* methylation (15/27) and for Stage III 44% (8/18).

(vii) P16 [54]. In a study of 45 individuals (25 with CRC and 20 healthy), methylation of *p16* was detected in 20% of patients, with a specificity of 100%.

(viii) TFPI2 [70]. Tissue factor pathway inhibitor 2 (TFPI2) is a polypeptide normally able to inhibit Factor Xa and IIa in the coagulation cascade. Using MS-PCR, fecal methylation of this protein's gene promoter was performed, and fluorescent quantitative real-time *Alu* PCR was used to determine the L-DNA quantity. Stool samples were retrieved from patients with CRC ($n = 60$), adenoma ($n = 20$), and healthy-control ($n = 30$). The specificity of this fecal molecular marker was 100%, with a sensitivity of 68.3%. When this fecal marker was combined with L-DNA analysis, a sensitivity of 86.7% was obtained.

(x) NDRG4 [71]. *NDRG4* gene on chromosome 16q21–q22.3 encodes for a protein of the same name, N-Myc downstream-regulated gene 4 (NMDRG-4). Unlike many CpG island promoter-methylated genes that are specific for a proximal or a distal tumour, hypermethylation of this gene is present in lesions at both sites. Methylation of the promoter of this gene evidenced in fecal material in patients with CRC ($n = 75$) and normal-control ($n = 75$) was assessed using quantitative MS-PCR. This marker yielded a sensitivity of 61% and specificity of 93%.

(xi) SFRP-1 [72]. Hypermethylation of this gene was detected in 29 patients with CRC, 7 with adenoma, and 17 normal-controls using MS-PCR with specially designed primers for methylated/unmethylated promoter sequences of *SFRP1*. This marker yielded an overall sensitivity of 89% and a specificity of 86%, and a significant difference was noted between patients with colorectal neoplasia and the normal-controls.

9. Multimarker Panels

With single genetic assays often yielding sensitivities and specificities to premalignant and malignant colorectal lesions lower than anticipated, some research has turned to the development of multimarker panels. To date, no single molecular marker has been identified that is expressed in all CRCs, and the genetic heterogeneity of these lesions suggest that a panel of molecular markers may be better suited for screening purposes [4, 6, 7, 73]. Studies that combine genetic and epigenetic markers have shown a higher sensitivity for colorectal lesions, though often at the expense of specificity [74]. Various combinations of markers have been attempted; however, the number and identity of markers to be included in order to obtain the desired sensitivity and specificity without significantly increasing costs remain undetermined [22]. The commonly studied multimaker panels are discussed below.

9.1. PreGen Plus. The best-studied multimarker panel is now commercially available under the name PreGen Plus. PreGen Plus has been available in the United States since 2003 and includes 21 point-mutations on *K-ras* (k12p.1, k12p.2, k12p.3), *APC* (876-2, 1306-2, 1309, 1312-1, 1367, 1378, 1379-3, 1450, 1465-8, 1554), and *p53* (175p.2, 245p.1, 245p.2, 248p.1, 248p.2, 273p.1, 273p.2, 282p.1) combined with BAT-26 and a DNA integrity assay (DIA) to detect abnormalities in the apoptosis pathway and detect L-DNA

Table 3: Studies of the PreGen panel in the detection of genetic alterations in fecal samples.

Authors and references	Markers	Specimen	Specimen n =	Control n =	Sensitivity	Specificity
Ahlquist et al. [32]	15 markers: Kras, APC, p53, BAT26, DIA	CRC Adenoma	22 11	28	91% 82%	93%
Berger et al. [75]	19 markers: p523, Kras, APC, BAT26	CRC	100	None	83%	NA
Berger et al. [76]	19 markers: p53, APC, KRAS, BAT26	Polyps ≥1 cm	32	None	88%	NA
Tagore et al. [23]	23 markers: full panel	Advanced CRC Adenoma	52 28	212	63.5% 57.1%	96.2%
Brand [36]	23 markers: full panel	CRC	16	None	69%	NA
Imperiale et al. [77]	23 markers: full panel	CRC Adenoma	31 40	1423	51.6% 32.5%	94.4%
Syngal et al. [78]	23 markers: full panel	CRC Adenoma	68 23	None	63% 26%	NA

[23]. This panel has been investigated by several authors, and their results are summarized in Table 3 with a brief discussion below.

(i) Ahlquist et al. (2000) [32]. This first multitarget panel studied only 15 markers in *Kras/APC/p53* + BAT-26 and DIA. Freezer-archived fecal samples from 22 patients with CRC, 11 with adenomas (≥1 cm), and 28 normal were retrieved,and sequence-specific hybrid capture was used to isolate human DNA. A sensitivity of 91% for CRC and 82% for adenomas was reported, with a specificity of 93%.

(ii) Berger et al. (2003) [75]. These authors used a panel of 19 mutations of *p53, K-ras,* and *APC* and BAT-26 deletions to evaluate the potential of fecal screening. Stool specimens from 100 patients without left-sided neoplasm distal to the splenic flexure were analyzed. 83% of these samples were positive for mutations.

(iii) Berger et al. (2003) [76]. This study did not include an assay for L-DNA; however, 19 markers on *p53, APC,* and *KRAS* were tested along with BAT-26 for their mutations in advanced colonic polyps larger than 1 cm in diameter. 28/32 of these polyps demonstrated one or more mutations (sensitivity 88%). Mutations were present in *Kras* (59%), *APC* (33%), and *p53* (22%) but not in BAT-26.

(iv) Tagore et al. (2003) [23]. Eighty patients with advanced CRC and 212 controls provided stool samples that were analyzed using this panel of molecular markers. The panel was able to identify 63.5% of invasive CRCs and 57.1% of advanced adenomas, 85.7% of which had high-grade dysplasia. The recorded specificity was 96.2% in patients with no lesions of the colorectum.

(v) Brand et al. (2004) [36]. Sixteen patients with CRC provided stool samples on three separate occasions prior to surgical resection. Samples were analyzed for 21 mutations of *p53, APC,* and *K-ras* and deletion of BAT-26. One or more mutations were identified in 11/16 patients (69%) in their first specimen, and there was a 93% concordance between results with positivity in sequential stools in 19/21 patients. A sensitivity of 69% was confirmed on their first specimen, and 86% subsequent stool specimens had identical mutations from the initial, with a 93% overall concordance between initial and subsequent stool analysis. The authors concluded that a single specimen is sufficient for fecal DNA molecular screening.

(vi) Imperiale et al. (2004) [77]. 4404 participants submitted a stool sample for DNA analysis using this panel, underwent FOBT (Hemoccult II) and a colonoscopy. This molecular marker panel detected 16/31 invasive cancers for a sensitivity of 51.6% and 13/40 with adenoma and high-grade dysplasia for a sensitivity of 32.5%. Overall specificity was 94.4% for this panel. Overall these results were more sensitive than the FOBT in this study.

(vii) Syngal et al. (2006) [78]. 91 patients with CRC ($n = 68$) and advanced adenomas ($n = 23$) gave stool samples prior to surgery, then 1–3 and 6–9 months after that. The three specimens were analyzed using this 23-marker panel. CRC specimens had a 63% sensitivity, and adenomas a 26%. 47% of all samples had two or more detected gene mutations. *Kras* was the most frequently identified mutation (41%), and distal lesions were more likely than proximal ones to have a positive test. 1–3 months post-op 18% of patients had positive results, and 12/14 were only positive for DIA. Many with these did not have DIA abnormalities prior to treatment, and it was suggested that chemoradiation and surgery may have increased L-DNA. At 6–9 months, only 7% remained positive, suggesting that removal of the neoplastic lesion causes DNA abnormalities to disappear.

(viii) Berger et al. (2006) [79]. This study examined the impact this commercial stool screening modality has on increasing adherence to CRC screening recommendations and identification of patients with CRC and adenomas. From 1211 participants, 87% found the specimen collection process easy to perform, and 91% reported that they would likely use the test again. An abnormal stool finding was correlated

with the detection of an abnormality at colonoscopy in 49% of patients.

9.2. Vimentin + DIA. The combination of *Vimentin* methylation and the presence of L-DNA, as detected by DIA, has been examined in the following studies.

(i) Itzkowitz et al. (2007) [34]. Forty patients with CRC and 122 normal/controls provided stool samples that had been immediately preserved with a buffer. A gel-based capture was used and analyzed for two separate panels: (a) 22 gene markers with DIA and (b) a combination of *Vimentin* with DIA. The combination (b) yielded the highest results, with an overall sensitivity of 87.5% and a specificity of 82%.

(ii) Itzkowitz et al. (2008) [8]. In this follow-up study, 42 patients with CRC and 241 normal-controls were assayed for hypermethylation of *Vimentin* and DIA. *Vimentin* was evaluated with MS-PCR andDIA with real-time PCR. Combined their sensitivity for CRC was 86% and specificity was 82%.

Additional multimarker panels that have been investigated in the literature include the following.

(iii) K-ras, p53, and APC [80]. Corpocytobiology techniques using colonocytes from fecal matter of 116 CRC patients and 83 normal-controls underwent both cytological examination and DNA analysis. An overall sensitivity of 71% was recorded, with 88% specificity.

(iv) K-ras, APC, Vimentin [81]. Point mutation on *KRAS,* scanned mutator cluster region of *APC,* and *Vimentin* methylation have been combined to create a molecular marker assay (panel 2) to be tested against the commercial 23-marker PreGen (panel 1) in a multicenter prospective triple-blinded trial. A total of 3764 adults underwent a screening colonoscopy, two FOBTs, and both of these molecular stool panels for analysis. On tissue examination, nearly all specimens analyzed contained at least one marker from the newly proposed panel (#2) whereas less than two-thirds of the tissue specimens contained markers from the commercial panel (#1). Recovery of these molecular markers in stool was nearly equal between the two panels (39% and 40% for panels 2 and 1, resp.). Stool DNA tests were conducted on fecal samples from 69 patients with screen-relevant neoplasia and 54 normal-controls. Panel 2 yielded higher positivity rates than panel 1, 43% versus 20%, including in CRC (58% versus 25%) and adenomas (45% versus 13%).

(v) K-ras, BAT-26, and TP53 [82]. Stool DNA from 51 CRC patients was retrieved, and the mutations to *p53, KRAS,* and BAT-26 were identified. The sensitivity for CRC of this panel was 71%.

(vi) APC, BAT-26, and L-DNA [83]. 57 CRC patients and 44 normal-controls provided stool samples for testing with this panel. Faecal material from 37 patients (65%) contained alterations of at least one of these molecular markers. This panel was found to have 14% higher sensitivity than FOBT.

(vii) RASSF2, SFRP2 [58]. The well-studied *SFRP2* was combined with methylation of *RASSF2* due to their high methylation rates in colon and gastric cancers. 788 colorectal and gastric tumour specimens were retrieved as well as 296 fecal specimens from both patients with neoplasia and controls. Extensive methylation of *SFRP2* and *RASSF2* was more common in colorectal tumours, with a sensitivity of 75% among CRC patients and 44% with advanced adenomas. A high false-positivity rate of 10.6% with a specificity of this assay was found to be 89.4%.

(viii) RARB2, p16, MGMT, and APC [74]. Promoter methylation of these four genes was analyzed initially in stool samples from 12 patients with newly diagnosed CRC, 20 with colorectal adenomas, and then from an additional 82 patients (20 healthy, 16 with inflammatory bowel disease, 20 with adenomas, and 26 with carcinomas). The first set was analyzed with MS-PCR and the second with methylation-specific melting curve analysis (MS-MCA). The first set yielded a sensitivity of 75% (9/12 patients) with carcinomas and 60% (12/20) with adenomas. In the second set, 62% of carcinomas (16/26) and 40% (8/20) adenomas were detected. The *RARB2* marker was positive in 13% (2/15) of stool samples in patients with inflammatory bowel disease. No methylation was detected in the "normal" group.

APC, ATM, hMLH1, SFRP2, HLTF, MGMT, GSTP1, and COX-2 [84]. Fecal samples from patients with CRC (n = 20), colorectal polyps (n = 30), and normal-controls (n = 30) were collected prior to colonoscopy. Using MS-PCR hypermethylation of *APC, ATM, hMLH1, sFRP2, HLTF, MGMT,* and *GSTP1* was analyzed, and COX-2 mRNA was detected using RT-PCR. This combination yielded a sensitivity of 75% in CRC and 68% in adenomas. A specificity of 90% was achieved as 3 normal-control patients were positive for at least one marker. COX-2 was only detected in 50% of cancer and 4% of adenoma patients.

ITGA4, SFRP2, and p16 [85]. This combination of markers was used to evaluate fecal specimens from 30 patients with CRC, 25 with adenoma, and 31 healthy-controls. Individually, *ITGA4, SFRP2,* and *p16* were detected in 36.7%, 60.0%, and 40.0% of CRCs and 16.0%, 44.0%, and 24.0% of adenomas, respectively. Combined, this multipanel yielded a sensitivity of 70.0% in CRC and 72.0% in adenoma. This combination yielded an overall specificity of 96.8%.

10. Advantages of Stool Testing

The advantages of testing stool samples for molecular markers as a screening test for precancerous and early-stage CRC are multifactorial. These include the following.

10.1. Improved Sensitivity and Specificity. The previously-established noninvasive screening technique FOBT and all

its subsidiaries rely on the presence of blood derived from a neoplasm in the stool. Comorbidities that may result in this fecal blood, such as active hemorrhoids or an extracolonic lesion, may be confounding [86]. Unlike bleeding that may be intermittent, colonocytes are continually being released and therefore a single specimen is sufficient [22, 73, 87]. Blood invasion is more common in later stages of CRC; however, release of tumour cells into the colonic lumen occurs earlier [7]. Sensitivity and specificity rates of stool DNA testing are higher for many markers [86]. Specificity is enhanced because, unlike serum tests, DNA does not enter the circulation, and heightened sensitivity may result from the large amount of DNA released from CRC compared with normal [22, 73]. This screening may accurately differentiate adenomas with the potential for transformation from purely benign entities. Psychological benefits to both the physician and the patient due to fewer false positives when compared to FOBT may result in improve acceptance and compliance to CRC screening [86].

10.2. Complete Screen. Fecal specimen contains genetic material representative of the entire colon, whereas sigmoidoscopy reaches only the distal third [86]. One study found a 20-biomarker panel to be sensitive to 83% of CRCs undetectable by flexible sigmoidoscopy [75] The screening interval may be increased as both cancers and precursor adenomas can be detected [86].

10.3. Small Amount of Specimen Required. Minute amounts of DNA can be detected and amplified over a billionfold using PCR [73, 87]. These can then be assessed for mutations.

10.4. Patient Friendly. Neither dietary nor medication restrictions are required in this screening; therefore, patient compliance is anticipated to increase [22, 81]. The procedure is more patient friendly, as it is noninvasive, requires no cathartic preparation, and does not necessitate an office visit as specimens can be mailed and stored [73, 86]. When in a buffer, stool samples can be transported and stored without degradation [22, 87]. Barriers such as travel, facility capacity, and labour are decreased in the patient-regulated process of specimen collection [8, 73, 86].

10.5. Ease of Use. 87% of patients in one study found the test easy to perform and 91% indicated they would be willing to take it again in the future [79].

10.6. Economical. The overall cost burden of CRC screening may decrease due to a limited number of required colonoscopies. The time interval between these exams may increase, and better identification of patients requiring this invasive screening will be more precise, decreasing the costs of unnecessary colonoscopies [5, 23, 86].

11. Disadvantages/Challenges of Stool Testing

The greatest challenge in faecal screening for CRC remains identification and selection of a single or panel of molecular markers with a high sensitivity and specificity. Many targets and combinations of molecular markers have been identified; however, which ones to use and how many of them remain undefined. This is further complicated by the understanding that the more markers used, the higher the cost [86]. Currently, molecular testing of stool specimens is expensive compared to FOBT [4], with the first stool DNA assay to reach market costing $795 [28]. Costs may be further elevated by the labour intensiveness of some of the described methodologies for genetic extraction and analysis [73]. However, cost issues, though very important, are very difficult to resolve. Further, with respect to current noninvasive tests such as FOBT, there is a significant difference in the execution times of the molecular genetic analyses. The dilemma still exists regarding accuracy of such tests versus their costs/benefits for large-scale use; these challenges remain largely unresolved. Such accurate methods are necessary in order to improve sensitivity and specificity.

Bile salts, hemoglobin degradation products, and complex polysaccharides in faecal specimens may act as inhibitors to PCR, and therefore special techniques are needed to circumvent this complication [58]. Finally, relatively high rates of false-positive and false-negative results limit the accuracy of these tests, thereby restricting their widespread use. False negatives may be due to PCR-based assays not detecting the hypermethylated DNA or due to colonoscopic exam missing a small adenoma. Four potential causes of a false- positive result include (i) experimental conditions of suboptimal standards, (ii) differences in the biology between populations from which normal fecal samples were obtained, (iii) subsistence of low levels of DNA methylation in normal tissue, and (iv) the detection of methylated genes from the normal colon/aberrant crypt foci rather than a relevant lesion [55].

12. Future

Detection of precancerous and early-stage CRC is central to improving patient prognosis. Currently available screening techniques have improved their sensitivity to cancerous lesions; however, detection of precursor adenomas with a potential to become malignant remains a challenge. The use of molecular markers in fecal specimens has increasingly become a potential screening tool. Multiple markers have been put forward, some with very promising sensitivity and specificity, yet further validation is required before they can be considered for generalized widespread use. More sensitive PCR strategies and modifications to stool preservation are additional factors that may improve the results of these studies [28]. Once a single/multiple panel of biomarker(s) have been identified, prospective studies with large sample sizes are required for evidence-based statistical assessment. Such tests should include FOBT in parallel for comparative purposes [19]. In the future, such techniques may extend to the detection of supracolonic aerodigestive cancers and aid in the diagnosis of inflammatory bowel disease [30]. Fecal molecular markers have the inherent potential to identify not only malignancies but also benign precursor-malignant entities with a high sensitivity and specificity, thereby coming

closer to the ultimate goal of reducing colorectal cancer incidence and mortality [7].

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