Choosing the optimal method in programmatic colorectal cancer screening: current evidence and controversies

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Abstract: Colorectal cancer (CRC) is an important health problem all over the world, being the third most common cancer and the second leading cause of cancer-related death in Western countries. The most important strategy for CRC prevention is screening (i.e. secondary prevention). Since it is widely accepted that adenomas and serrated polyps are the precursors of the vast majority of CRC, early detection and removal of these lesions is associated with a reduction of CRC incidence and, consequently, mortality. Moreover, cancers detected by screening are usually diagnosed at early stages and, therefore, curable by endoscopic or surgical procedures. This review will address CRC screening strategies in average-risk population, which is defined by those individuals, men and women, 50 years of age or older, without any additional personal or familial predisposing risk factor. In order to maximize the impact of screening and ensure high coverage and equity of access, only organized screening programs (i.e. programmatic screening) should be implemented, as opposed to case-finding or opportunistic screening. For that reason and considering that the optimal approach for colorectal screening may differ depending on the scenario, this review will be focused on the advantages and limitations of each screening strategy in an organized setting.

Keywords: biomarkers, colonoscopy, colorectal neoplasms, screening, fecal occult blood testing, flexible sigmoidoscopy

Colorectal cancer (CRC) is an important health problem all over the world, being the third most common cancer and the second leading cause of cancer-related death in Western countries. According to recent reports, it is the third most frequent neoplasm in men (663,000 new cases per year, 10.0% of the total) and the second in women (570,000 new cases per year, 9.4% of the total). Incidence rates vary 10-fold worldwide, the highest rates being observed in Australia/New Zealand and Western Europe, and the lowest in Africa and South-Central Asia. About 608,000 deaths from CRC were estimated worldwide in 2008, accounting for 8% of all cancer deaths [Ferlay *et al.* 2010].

CRC pathogenesis

The etiology of CRC involves the complex interaction of environmental carcinogen exposure and genetic factors in the population. Indeed, most

CRC cases are sporadic, occurring in individuals without any known familial predisposition. Approximately 10–30% of cases have a positive family history of this neoplasm [Castells *et al.* 2009], although the predisposing genetic factors involved in such a setting have not yet been identified [Tomlinson *et al.* 2008; Abuli *et al.*]. Highly penetrant inherited CRC syndromes are less common, accounting for only 5% of all CRC cases [Castells *et al.* 2009]. They can be divided into ‘polyposis’ and ‘nonpolyposis’ syndromes, being the first group subclassified into adenomatous, hamartomatous and hyperplastic polyposis [Balmana *et al.* 2010]. The most prevalent non-polyposis inherited form is Lynch syndrome, formerly known as hereditary nonpolyposis CRC, which accounts for up to 3% of the CRC burden and it is caused by germline mutations in the DNA mismatch repair genes [Piñol *et al.* 2005; Moreira *et al.* 2012].

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The transformation of normal colonic epithelium to cancer was originally assumed to take place through the accumulation of somatic genetic aberrations in a stepwise fashion following the stereotyped adenoma–carcinoma sequence [Fearon and Vogelstein, 1990]. Although this model is still valid, recent research has identified up to three main molecular pathways that result in malignant transformation of colonic epithelium, which are described as the chromosomal instability pathway, the microsatellite instability pathway, and the CpG island methylator phenotype pathway, each one characterized by the predominance of specific genetic and epigenetic changes [Castells *et al.* 2001; 2009; Harrison and Benziger, 2011; Jover *et al.* 2011].

CRC prevention

There are three strategies for CRC prevention [Levin *et al.* 2008; Castells *et al.* 2009; Segnan *et al.* 2010]. Primary prevention is aimed at decreasing the risk for developing this neoplasm and is mainly based on dietary and lifestyle modifications. It also includes chemopreventive measures, which has been defined as the use of natural, synthetic or biologic chemical agents to reverse, suppress or prevent the carcinogenic progression. In that sense, one of the most extensively evaluated approaches to CRC chemoprevention is the use of nonsteroidal anti-inflammatory drugs [Ferrandez *et al.* 2012].

The most important strategy for CRC prevention is screening (i.e. secondary prevention) [Winawer *et al.* 2003; Levin *et al.* 2008; Segnan *et al.* 2010]. Since it is widely accepted that adenomas and serrated polyps are the precursors of the vast majority of CRC, early detection and removal of these lesions is associated with a reduction of CRC incidence and, consequently, mortality [Levin *et al.* 2008]. Moreover, cancers detected by screening are usually diagnosed at early stages and, therefore, curable by endoscopic or surgical procedures [Dubé *et al.* 2007; Levin *et al.* 2008].

Finally, the third approach for CRC prevention is surveillance (i.e. tertiary prevention). This approach is aimed at minimizing the impact of already established colorectal neoplasms on the patient's prognosis and it is mainly based on endoscopic follow up after resection of CRC or adenomas [Rodriguez-Moranta *et al.* 2006; Winawer *et al.* 2006; Zauber *et al.* 2012; Castells *et al.* 2015].

Due to space constrictions, this review is focused on CRC screening strategies in average-risk

population, which is defined by those individuals, men and women, 50 years of age or older, without any additional personal or familial predisposing risk factor. Articles mentioned were selected based on their influence in changing clinical practice, with a positive discrimination of randomized clinical trials, meta-analyses, systematic reviews and clinical guidelines. Nevertheless, articles from the author's research group may be overrepresented in contextualizing the different aspects addressed in this review.

Programmatic CRC screening in a population-based scenario

The aim of population-based screening is to discover latent disease in the population to detect it in its early stages and enable it to be treated adequately. However, population screening targets an apparently healthy population and should, therefore, only be conducted after a careful consideration of both harms and benefits [Segnan *et al.* 2010].

To maximize the impact of screening and ensure high coverage and equity of access, only organized screening programs (i.e. programmatic screening) should be implemented, as opposed to case-finding or opportunistic screening [Segnan *et al.* 2010]. In fact, organized programs are recommended because they include an administrative structure responsible for service delivery, quality assurance and evaluation [Miles *et al.* 2004]. For that reason and considering that the optimal approach for colorectal screening may differ depending on the scenario, this review focuses on the advantages and limitations of each screening strategy in an organized setting.

Programmatic screening requires a high degree of organization in order to identify and personally invite each person in the eligible target population. Personal invitation aims to give each eligible person an equal chance of benefiting from screening and, therefore, to reduce health inequalities. In this context, the organizational framework allows an effective management and continuous improvement of the screening process since it includes linkage with population and cancer registries, thus optimizing both the invitation and evaluation of screening performance and impact [Segnan *et al.* 2010].

Evidence from several studies have shown that CRC screening is effective [Mandel *et al.* 2000;

Figure 1. Approaches to select those individuals who may benefit the most from colonoscopy (i.e. patients with colorectal cancer or advanced adenomas) in a population-based screening scenario.

Hewitson *et al.* 2008; Levin *et al.* 2008; Atkin *et al.* 2010] and cost-effective [Heitman *et al.* 2010] in the average-risk population. Recommended CRC screening strategies fall in two broad categories: stool tests, which include detection of occult blood and, more recently, exfoliated DNA; and structural examinations, which include flexible sigmoidoscopy and colonoscopy, among others [Winawer *et al.* 2003; Levin *et al.* 2008]. Search for occult blood in stools, using either the guaiac test or, more recently, the fecal immunochemical test (FIT) and flexible sigmoidoscopy, are predominantly implemented in Europe and Australia, where screening is mainly programmatic, whereas colonoscopy is the dominant screening modality in the US, where screening is mostly opportunistic [Segnan *et al.* 2010].

Colonoscopy

Colonoscopy is considered among the most appealing approaches for early detection and prevention of CRC [Winawer *et al.* 2003; Levin *et al.* 2008]. Although randomized studies evaluating its effect on CRC mortality are still lacking, it is recommended as a first-line screening modality on the basis of indirect data and observational studies. In fact, population-based case-control studies have suggested that colonoscopy decreases CRC incidence [Brenner *et al.* 2011a] and death [Baxter *et al.* 2009], whereas there is evidence indicating that patients with a previous negative colonoscopy have markedly reduced CRC risk [Imperiale *et al.* 2008; Brenner *et al.* 2011b, 2011c]. Recently, a meta-analysis of six observational studies evaluating the efficacy of screening colonoscopy in average-risk individuals concluded that this strategy was associated with a reduction in CRC incidence and mortality of 69% [relative risk (RR), 0.31; 95% confidence interval (CI),

0.12–0.77) and 68% (RR, 0.32; 95% CI, 0.23–0.43], respectively [Brenner *et al.* 2014]. Finally, cohort studies of patients with adenomas suggested that polypectomy could prevent up to 80% of CRC [Winawer, 1993; Citarda *et al.* 2001; Zauber *et al.* 2012].

Though colonoscopy plays a key role in all CRC screening modalities, not only in average-risk population [Lieberman *et al.* 2000, 2007a] but also in high-risk individuals [Castells *et al.* 2009; Vasen *et al.* 2015], it has some limitations and lesions can be missed at variable rates [van Rijn *et al.* 2006]. The adenoma detection rate (ADR), therefore, has become the most important indicator of the quality of colonoscopy [Kaminski *et al.* 2010] because it is directly related to key outcome parameters, such as interval cancer, and indirectly reflects other surrogate markers including quality of preparation, colonoscopy completeness and withdrawal time, as well as dedication and experience of the endoscopist. In an *ad hoc* analysis of the ColonPrev study, factors independently related to the ADR were a mean withdrawal time longer than 8 minutes [odds ratio (OR), 1.51; 95% CI, 1.17–1.96] and split bowel preparation (OR, 1.26; 95% CI, 1.01–1.57) [Jover *et al.* 2013].

Concerns about the use of colonoscopy as the primary screening method in a population-based scenario are the resources needed and potential complications. Indeed, it is estimated that the cost to screen the whole target average-risk population in Europe (i.e. approximately 146 million people) would exceed 3,650 million Euros annually. Moreover, in this scenario, although the rate of serious gastrointestinal side effects of colonoscopy (i.e. perforation and bleeding) is relatively small (2.4‰ [Warren *et al.* 2009]), the absolute number not be neglected from a public health perspective. Taking into account all these considerations and, more important, the fact that the prevalence of advanced neoplasm – the main target lesion in a CRC screening setting – in average-risk population does not exceed 10% of these individuals [Quintero *et al.* 2012a], the most rational approach could be to limit the use of colonoscopy to those people with the highest likelihood of presenting such lesions.

The selection of those individuals mentioned above who may benefit the most from being screened by colonoscopy relies on the concept of risk stratification, which can be established with different strategies (Figure 1). First, the use of

Table 1. Performance characteristics of fecal immunochemical testing for the detection of colorectal cancer.

Characteristics	Value	95% CI
Sensitivity	0.79	0.69–0.86
▪ <20 µg hemoglobin/g of feces	0.89	0.80–0.95
▪ 20–50 µg hemoglobin/g of feces	0.70	0.55–0.81
Specificity	0.94	0.92–0.95
Positive likelihood ratio	13.10	10.49–16.35
Negative likelihood ratio	0.23	0.15–0.33
Diagnostic accuracy	0.95	0.93–0.97
Modified from Lee <i>et al.</i> [2014]. 95% CI, 95% confidence interval.		

mathematical scores to estimate the likelihood of detecting advanced neoplasms at colonoscopy. Indeed, in the past few years, several models derived from regression analyses of large series of individuals undergoing colonoscopy have been proposed [Kaminski *et al.* 2014; Ma and Ladabaum, 2014; Wong *et al.* 2014]. With minor differences, most of them include age, gender, family history of CRC, cigarette smoking and body mass index. This approach can be useful in opportunistic screening, but it may be more difficult to implement it in an organized program. Second, it has recently been proposed to use genetic or genomic profiling to select those individuals mainly predisposed to develop colorectal neoplasms. In fact, common genetic variants (i.e. single nucleotide polymorphisms) identified in large whole-genome association studies seem to play a critical role in CRC development [Abuli *et al.* 2010; Dunlop *et al.* 2013], but its potential utility in risk stratification for screening purposes has not yet been demonstrated. Finally, the most common approach employed in programmatic screening is the use of 'non- or less-invasive' methods to select those individuals with a higher probability of presenting advanced neoplasms. In this scenario, fecal occult blood testing (FOBT) and flexible sigmoidoscopy are the most commonly used strategies, whereas the detection of molecular biomarkers of colorectal neoplasia in either blood or feces is emerging as an appealing alternative.

Fecal occult blood testing (FOBT)

FOBT has been demonstrated to reduce CRC mortality [Mandel *et al.* 1993; Hardcastle *et al.* 1996; Kronborg *et al.* 1996] and incidence [Mandel *et al.* 2000] in randomized controlled trials. Indeed, biennial guaiac-based FOBT is associated with a 16% reduction in CRC mortality (RR, 0.84; 95%

CI, 0.78–0.90) [Hewitson *et al.* 2007], which rises to 33% (RR, 0.67; 95% CI, 0.50–0.87) when the test is performed annually [Mandel *et al.* 1993]. Moreover, in the Minnesota trial, it was also demonstrated a reduction in CRC incidence of 20% (RR, 0.80; 95% CI, 0.70–0.90) and 17% (RR, 0.83; 95% CI, 0.73–0.94) when the test was performed in an annual or biennial basis, respectively [Mandel *et al.* 2000]. Likewise, several trials have confirmed the superiority of FIT over the guaiac-based tests (Table 1), which is especially noteworthy with respect to uptake and detection rate of advanced colorectal neoplasia [Guittet *et al.* 2007; van Rossum *et al.* 2008; Hol *et al.* 2009, 2010]. In fact, compliance to FIT is markedly increased compared with guaiac-based FOBT since there is no need of dietary restriction and obtaining one sample of feces is sufficient [van Rossum *et al.* 2008]. Moreover, FIT offers additional benefits, such as the production of numerical results that remove the subjectivity of interpretation, and automated processing which favors high throughput and precise quality assured programs.

The quantitative nature of FIT allows the selection of an optimal cutoff concentration for a specific target population, thus adjusting the positivity rate to local resources [van Rossum *et al.* 2008; Hol *et al.* 2009]. In a similar approach, FIT may contribute to identifying those individuals with higher risk for developing advanced colorectal neoplasms in order to prioritize them in programs with a large colonoscopy demand. In that sense, whereas the main cutoff of this test selects people who should undergo colonoscopy, the use of secondary cutoffs would allow stratification of them according to the probability of premalignant or malignant lesions. This approach has recently been demonstrated in a study in which fecal hemoglobin concentration, in addition to sex and

Table 2. Diagnostic yield* of both colonoscopy and fecal immunochemical testing obtained at the first round of the ColonPrev study.[‡]

Colorectal lesion	Colonoscopy (n = 26,703)	FIT (n = 26,599)	OR [‡]	95% CI	p value
Cancer	30 (0.1%)	33 (0.1%)	0.99	0.61–1.64	0.99
Advanced adenomas	514 (1.9%)	231 (0.9%)	2.30	1.97–2.69	<0.001
Advanced neoplasia	544 (2.0%)	264 (1.0%)	2.14	1.85–2.49	<0.001
Non-advanced adenomas	1109 (4.2%)	119 (0.4%)	9.80	8.10–11.85	<0.001
Any neoplasia	1653 (6.2%)	383 (1.4%)	4.67	4.17–5.24	<0.001

*Diagnostic yield: number of true positives relative to the number of eligible individuals.
[‡]The ColonPrev study is a randomized controlled trial comparing colonoscopy and biennial FIT for screening purposes in average-risk population [Quintero *et al.* 2012a].
[‡]According to the intention-to-screen analysis and adjusted by age, gender and participating center.
FIT, fecal immunochemical test; OR, odds ratio; 95% CI, 95% confidence interval.

age, was used to stratify FIT positive individuals according to their likelihood for the detection of advanced colorectal neoplasia [Auge *et al.* 2014].

However, it has been suggested that FIT-based screening is more effective than other screening strategies. Indeed, two studies have shown that FIT is better accepted than flexible sigmoidoscopy [Hol *et al.* 2010] or colonoscopy [Segnan *et al.* 2007] and, moreover, FIT has potential advantages for massive screening from a logistical perspective and overcomes colonoscopy regarding resources and related complications [Quintero *et al.* 2012a]. These circumstances have obvious implications in terms of human, technical and financial resources, which are critical in population-based screening program [Levin *et al.* 2008].

The baseline analysis of the ColonPrev study, a multicenter, nation-wide, randomized controlled trial performed in Spain, indicated that one-time screening with FIT was equivalent to colonoscopy to detect CRC in average-risk population in terms of diagnostic yield, detection rate and tumor staging, but colonoscopy was superior to FIT in detecting advanced and nonadvanced adenomas (Table 2) [Quintero *et al.* 2012a]. In this analysis, the FIT strategy was better accepted than colonoscopy, needed to scope five times fewer individuals to detect one advanced neoplasm, and had fewer complications [Quintero *et al.* 2012a].

Since advanced adenomas are usually considered a surrogate marker of CRC [Baron *et al.* 2003; Arber *et al.* 2006], the superiority of colonoscopy for detecting such lesions observed in the ColonPrev study [Quintero *et al.* 2012a] should

be considered a potential advantage for this strategy in terms of reducing not only CRC mortality but also CRC incidence [Lieberman *et al.* 2000]. However, it should also be taken into account that FIT detected as many as half of advanced adenomas in a single round, and considering that this strategy is based on periodical performance of the test every 1 or 2 years, it is feasible that the apparent advantage of colonoscopy will be reduced on the long term. On the other hand, the remarkable higher detection rate of colonoscopy for nonadvanced adenomas observed in the ColonPrev study [Quintero *et al.* 2012a] is more difficult to interpret. Most of these lesions, in fact, correspond to low-risk adenomas, with a natural history less predictable but unquestionably blameless than advanced adenoma [Lieberman *et al.* 2000, 2007b]. The long-term results of this study and other ongoing randomized controlled trials performed in the same scenario (i.e. NordICC [Kaminski *et al.* 2012] and CONFIRM studies) will definitively establish the impact of all these observations on CRC-related survival.

Flexible sigmoidoscopy

Flexible sigmoidoscopy has also demonstrated to reduce CRC incidence and mortality in randomized controlled trials [Atkin *et al.* 2010; Segnan *et al.* 2011; Schoen *et al.* 2012; Holme *et al.* 2014]. In the US trial [Schoen *et al.* 2012], screening with flexible sigmoidoscopy was associated with a 21% reduction in CRC incidence (RR, 0.79; 95% CI, 0.72–0.85), both in the distal (RR, 0.71; 95% CI, 0.64–0.80) and proximal colon (RR, 0.86; 95% CI, 0.76–0.97), and a 26% reduction in CRC-specific mortality (RR, 0.74; 95%

CI, 0.63–0.87), which is limited to those individuals with tumors located at the distal colon [Schoen *et al.* 2012]. In the SCORE trial [Segnan *et al.* 2011], performance of a single sigmoidoscopy at around the age of 60 years was associated with a 18% reduction in CRC incidence (RR, 0.82; 95% CI, 0.69–0.96), whereas the mortality rate was not significantly reduced (RR, 0.78; 95% CI, 0.56–1.08) compared with the control group in the intention-to-screening analysis. In the *per protocol* analysis, both CRC incidence (RR, 0.69; 95% CI, 0.56–0.86) and mortality (RR, 0.62; 95% CI, 0.40–0.96) were significantly reduced among screened subjects [Segnan *et al.* 2011]. In the UK trial [Atkin *et al.* 2010], CRC incidence was reduced by 23% (HR, 0.77; 95% CI, 0.70–0.84) and mortality by 31% (HR, 0.69; 95% CI, 0.59–0.82) with once-only flexible sigmoidoscopy. In the *per protocol* analyses, incidence of CRC in people attending screening was reduced by 33% (HR, 0.67; 95% CI, 0.60–0.76) and mortality by 43% (HR, 0.57; 95% CI, 0.45–0.72) [Atkin *et al.* 2010]. Finally, in the NORCCAP trial [Holme *et al.* 2014], CRC incidence was reduced by 20% (HR, 0.80; 95% CI, 0.70–0.92), and CRC mortality by 27% (HR, 0.73; 95% CI, 0.56–0.94).

Sigmoidoscopy-based CRC screening is founded on the fact that distal findings predict the risk of advanced proximal neoplasms [Read *et al.* 1997; Levin *et al.* 1999; Imperiale *et al.* 2000; Schoenfeld *et al.* 2005]. In that sense, there is general agreement that the magnitude of this risk is related to the histological features of the distal lesion (i.e. tubulovillous or villous adenoma, or with high-grade dysplasia), but the association with the adenoma size alone is more controversial [Read *et al.* 1997; Levin *et al.* 1999; Imperiale *et al.* 2000]. This circumstance has prompted a large variability among sigmoidoscopy-based strategies regarding the criteria used to refer for colonoscopy [Bretthauer *et al.* 2002; Atkin *et al.* 2010; Segnan *et al.* 2011]. Indeed, in the UK trial, criteria included one distal adenoma ≥ 10 mm, with villous component or high-grade dysplasia, three or more distal adenomas, or CRC [Atkin *et al.* 2010], while in the SCORE trial, the limiting size for distal adenomas was 5 mm [Segnan *et al.* 2011] and, in the NORCCAP trial, any adenoma was indicative for colonoscopy referral [Bretthauer *et al.* 2002]. Recently, the ColonPrev study has allowed comparison of risk estimations by simulating the sigmoidoscopy yield would have resulted from using these three sets of criteria to refer for colonoscopy based on the characteristics of distal

lesions [Castells *et al.* 2013]. In this *post hoc* analysis, the number of individuals fulfilling the NORCCAP and SCORE criteria were triple and double, respectively, than those fulfilling the UK criteria. In addition, whereas the NORCCAP criteria achieved the highest overall advanced neoplasm detection rate associated with the highest sensitivity for detecting advanced proximal neoplasms (APNs), the set of criteria proposed in the UK trial achieved the highest specificity and benefited from the lowest number of individuals needed to refer for colonoscopy [Castells *et al.* 2013].

Although demonstration of CRC-specific mortality and incidence reduction associated with the use of flexible sigmoidoscopy [Atkin *et al.* 2010; Segnan *et al.* 2011; Schoen *et al.* 2012; Holme *et al.* 2014], this strategy has long been criticized because of its lower ability to detect advanced proximal neoplasms with respect to colonoscopy [Imperiale *et al.* 2000; Lieberman *et al.* 2000; Podolsky, 2000]. Indeed, in the *post hoc* analysis of the ColonPrev study, simulated sigmoidoscopy-based strategies detected 35–43% fewer individuals with advanced neoplasms than colonoscopy, with a sensitivity for detecting APNs of 22–37% [Castells *et al.* 2013], similar to previous studies [Imperiale *et al.* 2000; Lieberman *et al.* 2000].

Fecal and plasma molecular biomarkers

In the past few decades, many molecular events participating in the initiation and progression of CRC have been elucidated. Unfortunately, this extraordinary progress has not yet impacted on the clinical setting. Therefore, there is a need to integrate the acquired knowledge on colorectal carcinogenesis into new strategies to prevent its onset and to establish an early diagnosis. In that regard, genetic and epigenetic changes can constitute noninvasive biomarkers if they are measurable in feces, blood or other biological fluids. In fact, exfoliation of neoplastic cells in feces is a continuum process in patients with CRC, whereas cancer cells and tumor-associated markers may reach systemic circulation favored by the angiogenic process.

The use of biomarkers for screening purposes could improve sensitivity, compliance and accessibility of current strategies. In that regard, biomarkers should be highly sensitive for early CRC stages and precursor lesions (i.e. advanced adenomas and serrated lesions) located in both

right- and left-colon side, highly specific to minimize the number of false positive results leading to unnecessary colonoscopies, noninvasive, user friendly, requiring neither bowel preparation nor diet restriction, affordable and widely distributable. To achieve these goals, several challenges need to be addressed. First, molecular heterogeneity at tumor level and the existence of different pathways involved in CRC pathogenesis (i.e. chromosomal instability, microsatellite instability and CpG island methylator phenotype) preclude the use of a single, unique molecular marker. Second, marker release differs depending on the biological scenario, since tumor cells and biomarkers are more likely to enter into stool at earlier stages than into blood or urine. Third, analytical sensitivity for detecting minimal quantities of the molecular marker in a huge amount of background DNA or diluted in an outsized volume of body fluids is a critical and limiting issue. Finally, but not less important, costs of production and implementation should also be taken into consideration.

Fecal DNA

Initial studies evaluating the use of stool-based DNA tests showed a disappointing sensitivity for the detection of colorectal neoplasms, specially advanced adenomas [Traverso *et al.* 2002; Imperiale *et al.* 2004; Chen *et al.* 2005; Itzkowitz *et al.* 2007]. However, in the past few years, important technical advances have been introduced, including better stabilizing buffers, more discriminating markers and more sensitive analytical methods, which have resulted in a higher sensitivity for the detection of both cancer and precancerous lesions.

Recently, the results of the DeeP-C study, the largest prospective randomized trial evaluating the usefulness of fecal DNA in CRC screening, have been published [Imperiale *et al.* 2014]. In this study, a new multitarget stool DNA test (Cologuard®, Exact Sciences, Madison, WI, USA), which includes quantitative molecular assays for *KRAS* mutations, aberrant *NDRG4* and *BMP3* methylation, and β -*actin*, plus a hemoglobin immunoassay, were compared with FIT for the detection of CRC and advanced precancerous lesions. Of the 9989 participants evaluated, 65 (0.7%) had CRC and 757 (7.6%) advanced precancerous lesions (either adenomas or sessile serrated polyps) on colonoscopy. The sensitivity for detecting CRC was 92.3% with

DNA testing and 73.8% with FIT ($p = 0.002$), whereas the corresponding figures for advanced premalignant lesions were 42.4% and 23.8%, respectively ($p < 0.001$). Interestingly, the rate of detection of serrated sessile polyps larger than 10 mm was 42.4% with DNA testing and 5.1% with FIT ($p < 0.001$). Specificities with DNA testing and FIT were 89.8% and 96.4%, respectively ($p < 0.001$). These results indicate that multitarget stool DNA testing detects more neoplastic lesions than FIT at expenses of more false positive results [Imperiale *et al.* 2014].

Blood-born biomarkers

The use of serum or plasma biomarkers has been advocated because it may favor screening uptake. For this purpose, two different kinds of molecules fulfill the above-mentioned CRC screening requirements. First, alteration of the normal DNA methylation pattern is an important epigenetic mechanism involved in the carcinogenic process [Esteller, 2008]. Aberrant DNA methylation patterns have been found in plasma or serum samples of CRC patients, suggesting a new class of potential biomarkers for screening [Mitchell *et al.* 2008]. Second, small noncoding RNAs are a class of nucleic acids that have been shown to play important roles in tumorigenesis. Among them, microRNAs (miRNAs) seem to have an enormous potential as noninvasive biomarkers, as shown by our group [Giraldez *et al.* 2013] and others.

Several studies have evaluated the potential usefulness of detecting circulating DNA methylation in CRC screening. As it is depicted in Table 3, most of them, especially those relying on panels of different genes, have demonstrated a relatively high sensitivity for CRC. However, results obtained with respect to adenoma detection are still quite poor.

So far, the only commercially available blood-born biomarker for CRC screening is *Septin9* (Epi proColon Assay®, Epigenomics, Germany). Table 3 shows the most relevant studies evaluating this marker. Unfortunately, the results of the PRESEPT study, the largest multicenter clinical trial aimed at assessing the ability of *Septin9* to detect CRC in average-risk population, were somewhat disappointing [Church *et al.* 2014]. In this study, evaluating 1516 participants, a standardized sensitivity for CRC detection of 48% (the corresponding values for CRC stages I to IV were

Table 3. Circulating DNA biomarkers in colorectal cancer screening.

Study	Biomarker	Sensitivity		Specificity
		CRC	Adenoma	
Grutzmann <i>et al.</i> [2008]	<i>Septin9</i> methylation	58%	18%	90%
Li <i>et al.</i> [2009]	<i>Vimentin</i> methylation	59%	–	93%
Lee <i>et al.</i> [2009]	Methylation panel of four genes (<i>APC</i> , <i>MGMT</i> , <i>RASSF2A</i> , <i>Wif-1</i>)	87%	75%	92%
deVos <i>et al.</i> [2009]	<i>Septin9</i> methylation	71%	–	89%
Cassinotti <i>et al.</i> [2011]	Methylation panel of six genes (<i>CYCD2</i> , <i>HIC1</i> , <i>PAX5</i> , <i>RASSF1A</i> , <i>RB1</i> , <i>SRBC</i>)	84%	55%	68%
Warren <i>et al.</i> [2011]	<i>Septin9</i> methylation	90%	12%	88%
Pack <i>et al.</i> [2012]	Methylation panel of five genes (<i>E-cadherin</i> , <i>APC</i> , <i>DAPK1</i> , <i>FHIT</i> , <i>SMAD4</i>)	60%	–	84%
Church <i>et al.</i> [2014]	<i>Septin9</i> methylation	48%	11%	92%
CRC, colorectal cancer.				

35%, 63%, 46% and 77%, respectively) and for advanced adenomas of 11%, with a specificity of 92%, were observed. These results indicate that *Septin9* can be detected in plasma of asymptomatic average-risk individuals undergoing screening, but also that the test requires improved sensitivity for the detection of early cancer and advanced adenomas [Church *et al.* 2014].

miRNAs are evolutionarily conserved, endogenous, small noncoding RNA molecules of 20–22 nucleotides that function as regulators of gene expression with a crucial role in different cell processes (i.e. development, differentiation, proliferation, and apoptosis) and in the initiation and progression of human cancer [Esquela-Kerscher and Slack, 2006]. In this context, every tumor type has shown significantly different miRNA profiles compared with normal cells from the corresponding tissue [Lu *et al.* 2005; Calin and Croce, 2006]. Moreover, recent reports have demonstrated that miRNAs are present in serum and plasma [Mitchell *et al.* 2008], being circulating levels stables, reproducible and consistent among individuals [Mitchell *et al.* 2008]. Therefore, expression profiling of circulating miRNAs shows great promise as a novel noninvasive strategy for CRC screening.

In a recent study, we investigated whether plasma levels of miRNA can differentiate patients with CRC or advanced adenomas from healthy individuals [Giraldez *et al.* 2013]. Following a

discovery/training/validation approach, it was possible to demonstrate that plasma miRNA expression profiles in patients with such lesions differ from those of healthy controls. More important, we identified a panel of six miRNAs (i.e. miR18a, miR19a, miR19b, miR15b, miR29a, and miR335) which are significantly upregulated in patients with CRC, differentiating them from controls with area under the receiver operating characteristic curve values ranging from 0.80 (95% CI, 0.71–0.89) to 0.70 (95% CI, 0.59–0.80). However, only miR18a was confirmed to be significantly upregulated in patients with advanced adenomas (area under the receiver operating characteristic curve value of 0.64 (95% CI, 0.52–0.75). These results suggest that patterns of miRNA expression may act as biomarkers for CRC, although they still have a limited value in identifying patients with premalignant lesions [Giraldez *et al.* 2013].

Cost-effectiveness of CRC screening strategies

The main purpose of cost-effective analysis is to provide reasonable estimates on the expected efficacy and convenience of health interventions to the policy makers and, in general, to the whole society [Quintero *et al.* 2012b]. In that sense, cost-effectiveness is critical when applied to health interventions aimed at the general population because of the relevance of both efficacy and cost outcomes.

With respect to CRC screening, cost-effective analyses have consistently shown the favorable profile of this approach, regardless of the adopted strategy. Such a favorable cost-effectiveness, as compared with other medical interventions (i.e. breast cancer screening), appears related with the possibility to prevent not only CRC mortality but also CRC incidence [Quintero *et al.* 2012b].

There are several cost-effective analyses evaluating the main strategies for CRC screening, especially FOBT, flexible sigmoidoscopy and colonoscopy, in the average-risk population. In all of them, compared with no screening, cost-effectiveness ratios for screening with any of these strategies were between 10,000 USD and 25,000 USD per life-year saved [Pignone *et al.* 2002]. Moreover, recent studies have demonstrated that CRC screening is not only cost-effective but also cost-saving [Lansdorp-Vogelaar *et al.* 2010].

However, when CRC screening strategies are compared with each other in an incremental cost-effectiveness analysis, no single optimal strategy emerges across the studies [Pignone *et al.* 2002]. In one study, colonoscopy appeared to be the most cost-effective approach because it reduced mortality at relatively low incremental costs [Sonnenberg *et al.* 2000]. In this study, screening with annual FOBT cost less but saved fewer life-years compared with colonoscopy. Similarly, flexible sigmoidoscopy every 5 or 10 years was less cost-effective than the other two screening methods [Sonnenberg *et al.* 2000]. In a second study, the most effective strategy was annual rehydrated FOBT plus sigmoidoscopy every 5 years, which resulted in an incremental cost-effectiveness ratio of 92,900 USD per life-year saved compared with annual unrehydrated FOBT plus sigmoidoscopy every 5 years [Frazier *et al.* 2000]. In this study, colonoscopy every 10 years was less effective than the combination of annual FOBT plus sigmoidoscopy every 5 years, but a single colonoscopy at age 55 years achieved nearly half of the reduction in CRC mortality obtainable with colonoscopy every 10 years [Frazier *et al.* 2000].

The more recent introduction of FIT has prompted a re-evaluation of cost-effectiveness of CRC screening strategies. Indeed, biennial guaiac-based FOBT, biennial FIT and once-only flexible sigmoidoscopy were compared within the Irish screening program [Sharp *et al.* 2012]. Again, all scenarios were highly cost-effective

compared with no screening. The lowest incremental cost-effectiveness ratio was found for flexible sigmoidoscopy, followed by FIT and guaiac-based FOBT. Compared with sigmoidoscopy, FIT was associated with greater gains in quality-adjusted life-years and reductions in lifetime cancer incidence and mortality, but was more costly, required considerably more colonoscopies, and resulted in more complications [Sharp *et al.* 2012].

In summary, CRC screening appears to be cost-effective compared with no screening, but a single optimal strategy cannot be determined from the currently available data [Pignone *et al.* 2002].

Conclusion

Although colonoscopy is the most appealing approach for CRC screening, its usefulness may be limited in a population-based scenario. However, FIT and flexible sigmoidoscopy are adequate options in programmatic screening, but determination of the comparative effectiveness with respect to colonoscopy in terms of CRC mortality reduction needs to wait for the results of ongoing randomized controlled trials. Finally, biomarker-based screening strategies may improve CRC prevention, with new generation stool DNA tests offering a high performance and blood-born tests promising a better compliance.

Conflict of interest statement

The author declares no conflict of interest in preparing this article.

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